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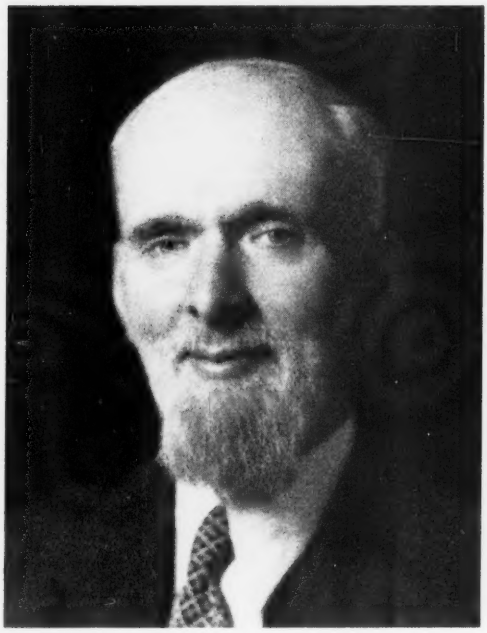


EVERT GORTER

In memoriam

When Dr. Gorter was confined to bed by his final illness some months ago, it became obvious to his disciples that soon his bereaved body would no longer be able to sustain his exceptional soul. In the night of the 16th February, 1954, Professor Dr. Evert Gorter passed away after a life of devoted service do mankind.

After taking his degree in 1905 and graduating *cum laude* in 1907, Gorter undertook the paediatric teaching at the University of Leiden, first as a private teacher, later as a lecturer, with a service of three beds on the medical ward and an out-patient department. At that time this was to be considered a precarious enterprise, because only a few enlightened minds were able to see in the child more than a miniature adult.

With incredible steadfastness and a tough perseverance characteristic of his entire life-time, he worked night and day, earning his livelihood as a child doctor. After a few years, thanks to the generosity of some friends to

whom we are indebted for ever, a couple of working-class houses were placed at his disposal; these he rebuilt. This little hospital was to be the birthplace of the famous children's clinic of Leiden. The destitution seemed to inspire him to ever-increasing activity and thus Gorter stood in the front line of investigators at the time when paediatrics came into full development.

He was appointed professor in 1923 and in 1927 he became head of a modern paediatric clinic; his ability as a leader was now generally acknowledged. Doubling his energy and interest, he effected the foundation of the Institute of Preventive Medicine and organized the paediatric teaching of the University of Gent. In addition, Gorter had set his mind to physico-chemical investigations the results of which are known the world over.

He was a talented orator, endowed with a profound knowledge of modern languages and a brain that always went to the root of the problem; he was a distinguished figure in international meetings, acknowledged as a leader and surrounded by a multitude of friends and admirers. His former assistants and collaborators literally formed a clan around this admired teacher.

But neither intellect nor scientific success, nor merits as a reformer of paediatrics and children's hygiene were the source of the admiration that everyone had for this exceptional fellow-man. Nor could Gorter be called affable; on the contrary, he always unintentionally kept himself at some distance, and only a few of his contemporaries could really call themselves his friends. But his human qualities; his simplicity, his ascetic soberness, his indomitable energy, his keen criticism of himself and of others,—a criticism without harshness—were some of the many causes of the admiration and the affection of his collaborators. Even when absorbed in his own investigations, Gorter was approachable for all difficulties, large and small, and a solution was always forthcoming.

His aim in life, the well-being of children, he restlessly pursued, even in his scientific investigations. By doing so he earned the gratitude of all Dutch mothers. But he was not in search of honour, of personal possessions or of economical profit. Even social intercourse and recreation were purposely avoided, because he feared that selfishness might lead him away from his love for mankind. And so Gorter was, like all great men, a lonely man in spite of all his admirers.

The incurable illness which caused a physical immobility, he endured as a saint: he never complained, nor did he let his illness inhibit his mental activities. If the spirit ever dominated the body, it did so here.

And now Gorter has passed away to a better life, where Our Lord, Who is always giving more than receiving, will grant him the rest he never allowed himself, and the enlightenment he has always sought.

Nymegen, April, 1954.

J. Slooff

Acta Pædiatrica **43**: 221—234. May 1954

From the Pediatric Clinic (Head: Professor STURE SIWE) and the Medical Clinic (Head: Professor HAQVIN MALMROS), University of Lund, Sweden.

Studies on Lipids, Proteins and Lipoproteins in Serum from Newborn Infants

by STURE RAFSTEDT and BENGT SWAHN

Introduction

The concentration of lipids in the blood of normal newborns is lower than in adults. HERRMANN and NEUMANN (1912) showed that the level of the cholesterol esters as well as that of neutral fat is lower in blood from the umbilical cord than in normal women. In 1924 GYÖRGY found decreased total serum cholesterol and lipid phosphorus in umbilical cord blood. HORNUNG (1926) was the first to report the increase of the serum cholesterol level during the first few days after birth. He found the total serum cholesterol in cord blood to be on an average 62 mg/100 ml, as against 90 mg/100 ml in infants 5—7 days old. HORNUNG gave the average total serum cholesterol as 160 mg/100 ml for normal adults. GYÖRGY showed that both the total serum cholesterol and the lipid phosphorus increase with age, and that the increase is most striking during the first month of life, when the total serum cholesterol increases from 80 to 125 mg/100 ml and the lipid phosphorus from 4.1 to 6.4 mg/100 ml. The increase of the total serum cholesterol during the first month of life was confirmed by SPERRY, who used the SCHOENHEIMER-SPERRY method. HODGES, SPERRY and ANDERSEN demonstrated that the total serum cholesterol reaches the adult level during the second month of life. HELLMUTH studied the total serum cholesterol, free cholesterol, total fatty acids and phospholipids in the sera from blood of 30 umbilical cords. He found the concentrations of all the lipid fractions to be significantly lower than in normal adults. The lipid values recorded in four infants delivered by Caesarian section were just as low as those found in the sera from the 30 children delivered by the normal route.

In electrophoretic studies of serum from umbilical blood (Tiselius' macroelectrophoresis), LONGSWORTH *et al.* (1945) found that the α- and β-globulin components were smaller than in pregnant women or in normal adults. As the α- and β-globulins contained the major part of the serum lipids (BLIX,

TISELIUS and SVENSSON), they made quantitative determinations of the total cholesterol and total lipids in these components. They found the lipid content of these components lower when they were isolated from serum from cord blood than when they were separated from serum obtained from normals or from pregnant women.

Ultracentrifugal determinations of the concentration of certain lipoprotein molecules (S_f 10–20 class) were reported by KEMPE *et al.* for 147 children ranging in age from birth to 15 years. The levels of these lipoproteins in cord blood (in 51 newborn infants) were of the same magnitude as those found in the total group of children.

On account of the large quantities of serum necessary for complete quantitative determination of serum lipids and lipoproteins, the serum has not been studied for changes in the concentration of the lipid fractions during the first few days of life. A micromethod for the determination of the serum lipids after electrophoretical separation on filter paper has been devised by SWAHN, who also described a micro-method for determining the total serum lipids.

A quantity of 0.6 ml serum was sufficient for the performance of the following determinations.

1. Determination of the relative concentrations of the serum proteins by the method for paper electrophoresis described by KUNKEL and TISELIUS [0.01 ml].
2. Determination of the total lipids (18) [0.02 ml].
3. Determination of the relative concentration of the lipids after electrophoretical separation (17) [0.02 ml].
4. Determination of the total cholesterol and free cholesterol by the method of SCHOENHEIMER and SPERRY [0.50 ml].
5. Determination of lipid phosphorus by a modification of BRUN's method.

Material

The series consisted of 50 infants. Blood specimens had been collected from every child at birth (umbilical cord blood) and again 1–6 days after birth (capillary blood). The birth weights of the children ranged from 2,500 to 5,150 g. Only children born at term and of healthy mothers were accepted. Delivery had been uncomplicated throughout. From birth until the collection of the second sample the children had been fed on mother's milk only. The series included only healthy infants.

Methods

Quantitative determination of the total cholesterol, free cholesterol, and phospholipid

The serum lipids were extracted by the method of SCHOENHEIMER and SPERRY. A quantity of 0.5 ml serum was extracted with 10 ml boiling ethanol and acetone in equal parts, filtered, and the following quantities of the extract were used for the different determinations: 1 ml for the determination of the total cholesterol, 2 ml for the determination of the free cholesterol, and 4 ml for the determination of the lipid phosphorus.

The total cholesterol and the free cholesterol in the extract were determined by the method of SCHOENHEIMER and SPERRY. The colorimetric analysis was performed with the aid of a Beckman spectrophotometer at 610 mμ in a 1 cm cuvette.

The lipid phosphorus was measured by a modification of the method described by BRUN (1939). Four ml of the ethanol-acetone extract were transferred to a small glass beaker in which it was protected from contamination with dust and evaporated on a water bath, which was maintained at a temperature of at most 50 C. The lipids were reextracted with 3 ml of petroleum ether (3 times) which was afterwards evaporated in a 30 ml Kjeldahl flask. The lipids were ashed with 0.2 ml of concentrated sulphuric acid and 0.2 ml of concentrated nitric acid. The ashed material was transferred with the aid of distilled water to a graduated flask (10 ml) in which it was diluted to a volume of 10 ml. Of this, 4 ml were transferred to a test tube to which 2 ml of amidol solution and 2 ml of molybdate solution were added. The intensity of the blue colour that developed was read in a Beckman spectrophotometer at 720 mμ in a 1 cm cuvette. The lipid phosphorus value multiplied by the factor 25 gives the concentration of the phospholipids in milligrams per hundred millilitres. This modification gives values in agreement with those obtained when using the method described by BRUN.

The concentration of the total lipids was determined according to SWAHN. The different serum protein fractions were studied with the aid of the paper electrophoresis method described by KUNKEL and TISELIUS. The relative concentrations of the lipoproteins were assessed by the method of SWAHN.

Results

The lipid fractions analysed in the present series (50 cases) were the total lipids, the total, esterified and free cholesterol and the phospholipids. Cord blood and capillary blood collected 1–6 days after birth were studied.

Fig. 1 shows that there is an increase of the total lipids in serum during the first days after birth. The figure demonstrates this increase in the first 22 cases examined. In all the other cases the same changes in total lipids can be seen. These 22 cases are thus representative for the material. (In order to give a better reproduction of the figures only this part of the material has been graphically presented.) Fig. 1 also shows the great variations in the individual cases. No correlation has been stated between time after birth and the increase of the total lipids. The wide variation range for the total lipids in cord blood as in capillary blood is demonstrated in Table 1. The table shows that some of the infants have higher values in cord blood than other infants in capillary blood some days after birth. The mean value for the increase of total lipids in all the 50 cases is about 70 per cent, which is statistically highly significant. All that has been said about the total lipids applies also for the total cholesterol (Fig. 2). In all cases there is an increase of the values during the first few days after birth. In one case there has been found a parallel increase of the total lipids and the total cholesterol. Table 1 shows the mean value for the total cholesterol in cord blood and in capillary blood some days after

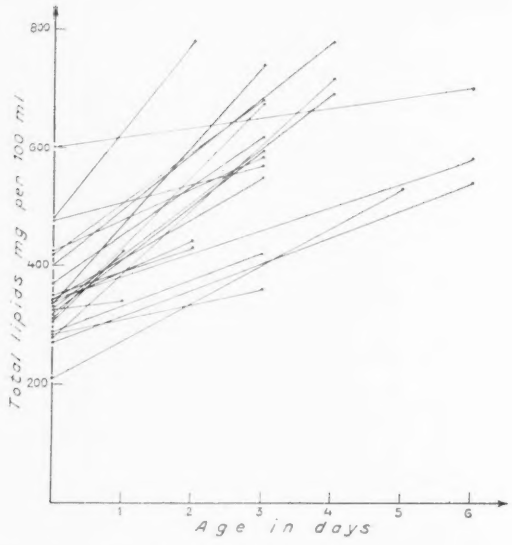


Fig. 1. The diagram represents the increase of total lipids in serum one to six days after birth. The values at zero on the abscis are those for cord blood.

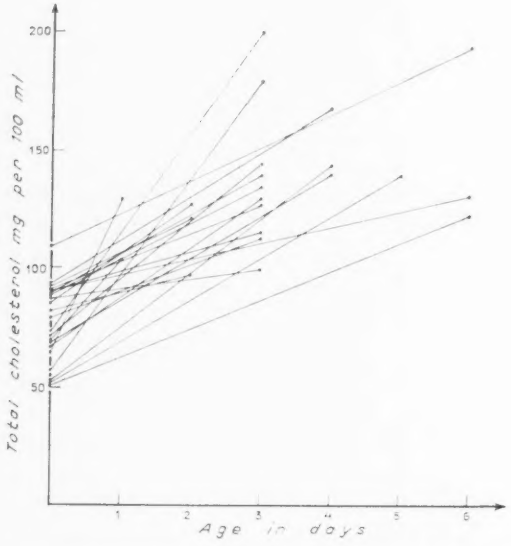


Fig. 2. The figure illustrates the increase of total cholesterol after birth.

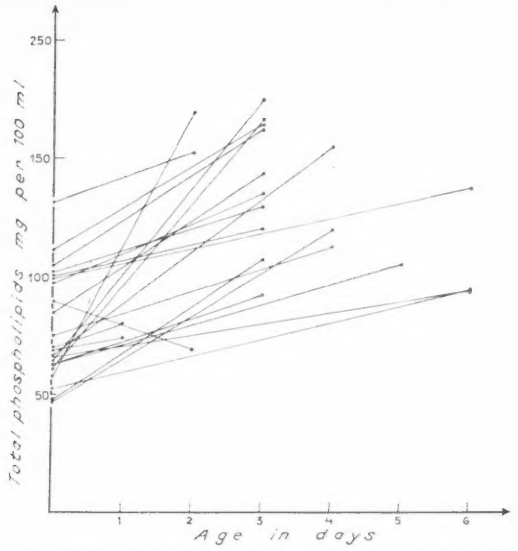


Fig. 3. The figure illustrates the increase of phospholipids after birth.

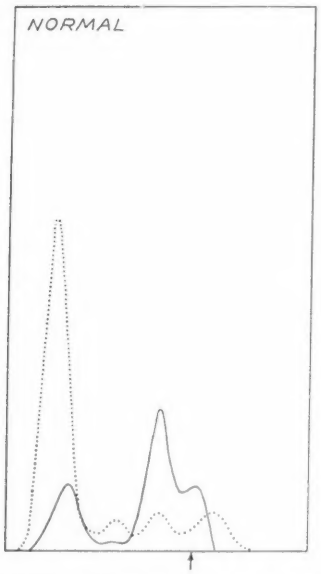


Fig. 4. Diagram showing the separate protein (dotted line) and lipid (solid line) components in a 17 years old woman. The high peak in the extreme left in the protein diagram is albumin. The lipid diagram shows four peaks: α_1-, α_2-, β- and in the extreme right the "chylomicron"-peak. The starting point is marked by an arrow.

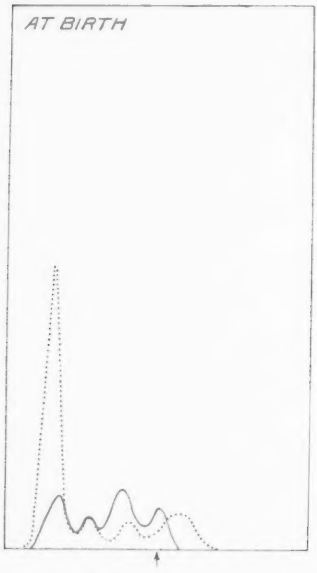


Fig. 5. Diagram showing the separate lipid and protein components in serum from cord blood

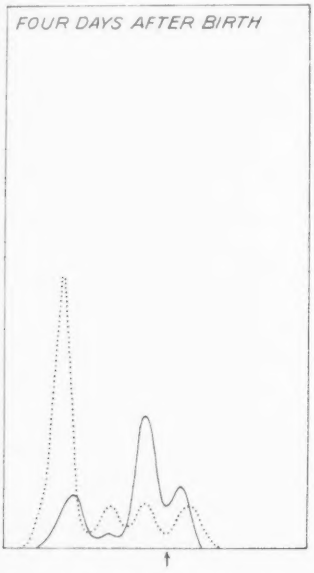


Fig. 6. Diagram showing the separate lipid and protein components in serum from the same infant as in fig. 2, four days after birth.

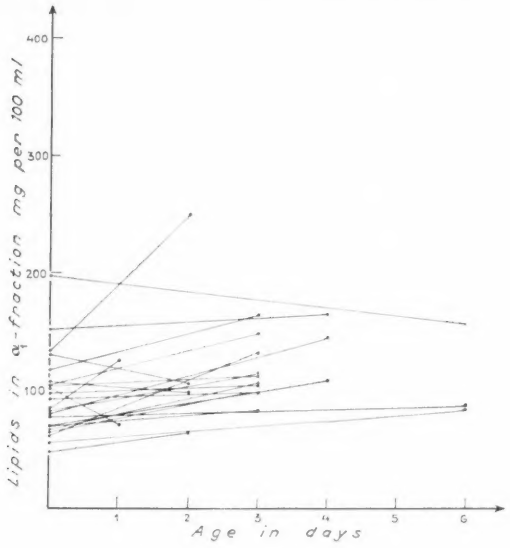
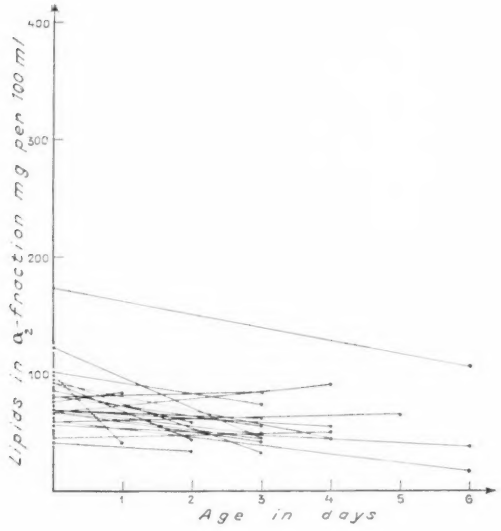


Fig. 7. The lines connect two determinations of lipids in α_1-fraction on the same infant.



8. The lines connect two determinations of lipids in α_2-fraction on the same infant.

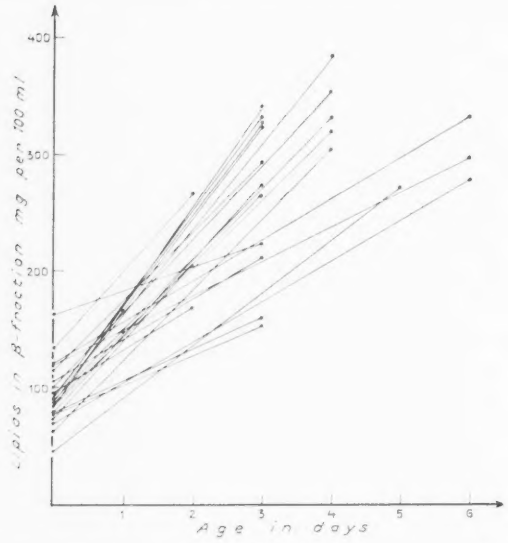


Fig. 9. The increasing values for lipids in β-fraction are shown by the lines.

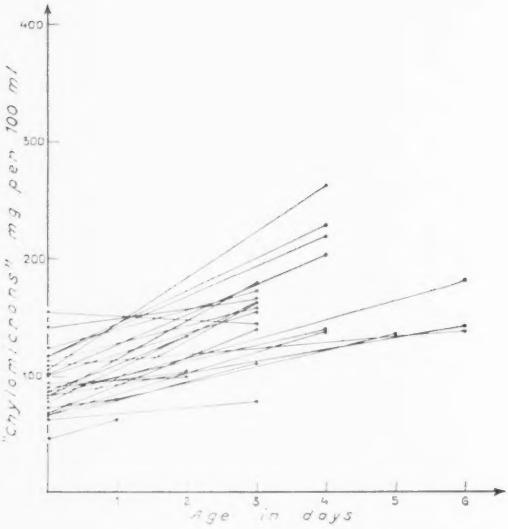


Fig. 10. The increasing values for lipids in the "chylomicron"-fraction are shown by the lin

birth. The increase of the mean value is about 80 per cent. Esterified and free cholesterol also show increased values after birth in all cases. The most striking increase is seen in the free cholesterol (more than 100 per cent). The changes of the phospholipids in serum after birth are represented in Fig. 3. One case shows a decrease. This value may be interpreted as an analytical error. All the other lipid fractions in this case show an increase of the same magnitude as in most other cases. The increases in the various lipid fractions are statistically highly significant.

Fig. 4 shows the concentrations of proteins and lipoproteins in serum from normal adults. Fig. 5 shows the corresponding concentrations for umbilical cord blood. It is apparent that the values are lower than for adults. This applies in particular to the β-fraction and the unmigrated "chylomicron"-fraction at the starting point, which probably consists of a mixture of highly molecular lipoproteins including chylomicrons which are adsorbed by the paper. The α_1-fraction was also low, but the small fraction corresponding to the α_2-globulin did not differ significantly from that found in adults. The α_1- and the β- and the "chylomicron"-fractions are of about the same magnitude in serum from cord blood. Fig. 6 shows the relative relationship between the various lipid fractions measured in sera collected 4 days after birth. Comparison with Fig. 1 shows that the lipid fractions had increased so much during the first few days of life that they had practically reached adult level. The α_1-fraction had markedly increased, but the most striking increases were recorded for the β- and the "chylomicron"-fractions.

Table 2 shows the mean values for the different lipoprotein fractions. The α_1-fraction is reproduced diagrammatically in Fig. 7. It shows an increase which is rather moderate in most cases. In some cases, indeed, there is a decrease. The increase in the mean values for the α_1-fraction in cord blood

TABLE 1.

Serum lipids in 50 newborn infants.

Mg/100 ml	Cord blood		Capillary blood 1–6 days after birth	
	mean value	range	mean value	range
Total lipids	347 ± 11	210–600	591 ± 18	340–890
Total cholesterol	75 ± 2	50–110	138 ± 4	98–200
Esterified cholesterol	53 ± 2	28–81	88 ± 3	37–137
Free cholesterol	22 ± 1	13–34	50 ± 2	25–105
Lipid phosphorus	3.0 ± 0.1	1.9–5.3	5.2 ± 0.2	2.8–7.1
Phospholipids	75 ± 3	48–133	131 ± 4	70–178

TABLE 2.

Proteins and lipoproteins in serum from 50 newborn infants.

	Cord blood		Capillary blood 1–6 days after birth	
	mean value	range	mean value	range
Mg/100 ml				
Lipids in α_1-fraction	103 ± 5	48–198	140 ± 6	71–264
Lipids in α_2-fraction	57 ± 5	14–174	44 ± 3	22–94
Lipids in β-fraction	105 ± 4	46–191	265 ± 10	148–460
Lipids in "chylomicron"-fraction	83 ± 4	46–154	141 ± 6	61–260
Per cent				
Albumin	71.5 ± 3.5	66–79	70.3 ± 3.5	63–78
α-globulin	6.1 ± 1.3	4–10	7.1 ± 1.4	5–9
β-globulin	7.2 ± 1.3	5–10	10.0 ± 2.0	7–16
γ-globulin	15.0 ± 2.4	10–19	12.5 ± 2.1	8–16

and capillary blood is statistically highly significant. The lipid fraction corresponding to α_2-globulin did not change significantly during the first days of life. A graphical reproduction of the α_2-fraction in the first 22 cases examined is given in Fig. 8.

The most striking increase is found in the β-fraction. This increase has been found in all the cases and is graphically reproduced in Fig. 9. The increase is statistically highly significant.

Also the "chylomicron"-fraction shows an increase which is statistically highly significant. The graphical reproduction in Fig. 10 shows, among the first 22 cases examined, only a single case with decreasing values.

All of the sera were also analysed for the relative concentrations of proteins. Table 2 gives the mean values and the ranges of variation. The albumin fraction does not show any statistical changes. Both the α- and β-fractions show a highly significant increase, while the γ-fraction shows a highly significant decrease. (The values are not corrected for differences in the dye-binding capacity of the different proteins.)

Discussion

Thanks to the micromethods referred to above it was possible to make a more complete analysis than hitherto of the increase in serum lipid fractions during the first few days of life.

A survey of earlier analyses of sera from umbilical cord blood and from blood collected during the neonatal period is given in tabular form (Table 3).

TABLE 3.

Author	No. of cases	Total lipids mg/100 ml	Total cholest. mg/100 ml	Esterif. cholest. mg/100 ml	Free cholest. mg/100 ml	Phospholipids mg/100 ml	Total fatty acids mg/100 ml	Lipoproteins	Remarks
Serum from umbilical cord blood									
1924 HORNUNG . .	20	—	62	29	33	—	—	—	Serum
1924 GYÖRGY . .	6	—	69	—	—	95	—	—	Serum
1926 GYÖRGY . .	14	—	80	—	—	103	—	—	Serum
1926 HELLMUTH .	30	660	70	40	30	110	150	—	Serum
1928 GORDON . .	16	—	89	—	—	103	—	—	Serum
1936 BOYD	29	198	34	20	14	61	140	—	Oxalated blood
1936 SPERRY . . .	6	—	61	—	—	—	—	—	Heparin blood
1954 RAFSTEDT & SWAHN	50	347	75	53	22	75	—	+	Serum
Serum from children during the first month of life									
1924 HORNUNG . .	20	—	80	33	47	—	—	—	3 d. aft. b.
1924 HORNUNG . .	20	—	90	51	39	—	—	—	5 7d.aft.b.
1926 GYÖRGY . .	10	—	124	—	—	155	—	—	During the first month
1928 GORDON . .	16	—	87	—	—	105	—	—	During the first week
1936 SPERRY . . .	63	—	133	86	46	—	—	—	4 24 days aft. birth
1954 RAFSTEDT & SWAHN	50	591	138	88	50	130	—	+	1 6d.aft.b.

All of the lipid values reported by BOYD were lower than those found by any of the other investigators. BOYD himself pointed out that "oxalated blood gives lower values for lipids in the plasma than does heparinised or defibrinated blood". SPERRY and SCHOENHEIMER also showed that serum and heparinised plasma contain one and the same amount of cholesterol, while oxalated plasma contains much less. All investigators found the lipid values for cord blood to vary widely from one case to another. All workers in this field who used defibrinated or heparinised blood found approximately equal mean values. In view of the wide individual variation in the lipid values, repeated examinations on one and the same child provide the best method for following changes in the lipid fractions. The two investigations including repeated examination of one and the same child (SPERRY and the present study) showed the total cholesterol concentration to increase by about 70

per cent during the first few days of life. All of the cholesterol values fo serum from blood collected after birth were in good agreement with thos reported by SPERRY, who used the same method of analysis. The number o cases in these series is so large that the mean value obtained may be regarde as reliable. In 63 children, aged 4 to 25 days, SPERRY found the total choles terol to range from 71 mg/100 ml to 190 mg/100 ml. In the present series o 50 children, aged 1 to 6 days, the corresponding values were 98 mg/100 m and 200 mg/100 ml. As the values for total cholesterol in umbilical cord bloo varied in the present material from 51 mg/100 ml to 110 mg/100 ml, th cholesterol level recorded at birth in some cases was higher than that recorde a few days afterwards in others. In every case the concentrations of the tota cholesterol, the free cholesterol and the phospholipids showed a pronounce increase during the first few days of life.

The concentration of the total lipids likewise showed a striking increas (about 65 per cent).

Repeated analysis of the serum for changes in the lipid fractions showe that of the general increase of the lipids during the first few days of life tha of the β-fraction is most striking. The α_1-fraction showed a moderate but significant increase. The fraction referred to in this paper as "chylomicrons" also increased and thereby indicated an increased amount of neutral fat in the blood.

It is not known whether these increases in the lipid fractions are ascribable to the child's diet after birth or to some unknown extra uterine adjustment process. Further studies are in progress to determine any changes in the serum lipids with increasing age.

Summary

With new micromethods it has been possible to determine in 0.6 ml serum the concentration of total and free cholesterol, phospholipids, and total lipids, and to perform electrophoretic separation of the protein fractions as well as of the various lipid fractions. Sera from blood of the umbilical cord and from capillary blood from 50 infants 1–6 days old were analysed. The cholesterol, the total lipids and the phospholipids increased 70–80 per cent during the first few days of life. The marked increase in the lipids in the serum after birth was ascribable above all to the striking increase in the β-fraction, but also to the lipids in the fraction termed "chylomicrons". The α_1-fraction showed a moderate but statistically significant increase. During the first few days of life the α- and β-globulins showed a statistically significant increase while the γ-globulin showed a statistically significant decrease. The albumin fraction did not change significantly.

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Études des lipides, protides et lipoprotéines du sérum des nouveaux-nés.

Les nouvelles microméthodes ont permis de déterminer dans 0,6 ml de sérum, le taux de cholestérol total et libre, de phospholipides, de lipides totaux, et de réaliser une séparation électrophorétique des diverses fractions protéiques, et des différents lipides. Des sérums provenant du sang de la veine ombilicale, ou du sang capillaire de 50 enfants de 1 à 6 jours ont été analysés. Le cholestérol, les lipides totaux, et les phospholipides s'accroissent de 70 à 80 % au cours des premiers jours de la vie. L'augmentation importante des lipides dans le sérum après la naissance paraît surtout due à la fraction β, mais également aux lipides de la fraction appelée «chylomicrons». La fraction α_1 montre une augmentation modérée, mais statistiquement significative. Au cours des premiers jours de la vie, les globulines α et β montrent également une augmentation statistiquement probante, tandis que les γ-globulines montrent une diminution parallèle. La fraction albumine ne s'est pas modifiée de façon significative.

Studien über Lipoide, Proteine und Lipoproteine im Serum Neugeborener.

Mit Hilfe neuer Mikromethoden war es möglich, in 0,6 cc Serum die Konzentration des totalen und freien Cholesterols, der Phosphorlipoide und der totalen Lipoide zu bestimmen, und außerdem die elektrophoretische Trennung der Proteinfraktionen und der verschiedenen Lipoidfraktionen durchzuführen. Bei 50 Säuglingen im Alter von 1 bis 6 Tagen wurden Serumanalysen des Nabelvenenblutes und des Kapillarblutes durchgeführt. Cholesterol, die totalen Lipoide und die Phosphorlipoide waren in den ersten Lebenstagen bis zu 70–80 % erhöht. Die nach der Geburt auftretende Vermehrung der Serumlipoide betraf vor allen Dingen die β-Fraktion, aber auch die Lipoide in der als „chylomicrons" bezeichneten Fraktion. Die α_1-Fraktion zeigte eine mäßige, aber doch statistisch signifikante Vermehrung. In den ersten Lebenstagen zeigten die α- und β-Globuline eine statistisch signifikante Vermehrung, während die γ-Globuline eine statistisch bedeutende Verminderung zeigten. Die Albuminfraktion veränderte sich nicht wesentlich.

Estudio de los lípidos, proteínas y lipoproteínas en el suero de niños recién nacidos.

Mediante nuevos micrométodos ha sido posible determinar, en 0,6 ml de suero, la concentración de colesterol libre y total, fosfolípidos y lípidos totales, y efectuar el fraccionamiento electroforético de las proteínas y de los lípidos. Se analizó el suero de sangre del cordón umbilical y sangre capilar en 50 recién nacidos, de 1 a 6 días de edad. El colesterol, los lípidos totales y fosfolípidos aumentaron en un 70–80 % durante los primeros días de la vida. El marcado aumento en los lípidos del suero después del nacimiento se atribuye especialmente al notable aumento en la fracción β, pero también al incremento de la fracción denominada „chylomicrons". La fracción α_1 mostró un aumento moderado pero estadísticamente significativo. Durante los primeros días de la vida las α y β globulinas demuestran un aumento estadísticamente significativo, mientras que la γ globulina experimenta una reducción estadísticamente significativa. La fracción de las albúminas no sufre cambios significativos.

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Height and Weight of Schoolboys at a Stockholm Secondary School, 1950, and a Comparison with Some Earlier Investigations

by ERNST ABRAMSON and EVA ERNEST

It has long been recognized that children from the poorer classes of the community, at corresponding ages, are as a rule shorter and lighter than children from better-class homes. In many cases this difference has coincided with nutritional conditions which are to some extent influenced by the financial circumstances of the home. Earlier investigations have not, however, taken the family income into account, but have been restricted to a comparison of children from elementary and secondary schools. In so doing it has undoubtedly been taken for granted, at least in the past, that the former children came from less prosperous homes than the latter. It is also possible that the differences observed in height and weight are dependent on hereditary factors or on environmental conditions other than those reflected by financial status. The social class from which the children come can therefore be of interest in this connection. The following investigations have been carried out in order to throw some light on these problems.

The material for this investigation is taken from Södermalm secondary school in Stockholm and covers all the pupils comprising 912 boys. Of these, 23 have been excluded from the statistical treatment since they were foreigners, 16 because complete information could not be obtained, and 2 because they were the only ones in the 21 year-old group. The material under treatment thus comprises 871 boys. Information regarding pupils' height, weight and date of birth has been taken from the health cards. The height and weight measurements were undertaken during September 1950, with the exception of a few cases which were investigated in March 1951. The age groups are so classified that children born, for example, during the period April 1st, 1932 to March 31st, 1951, are recorded under the ages of 17.5–18.5 years, etc. Information regarding parents' incomes has been taken from the income tax records. Taxes have been deducted from the gross income with a view to give a clearer conception of the family's economic situation than would be obtained from the gross family income alone. Children's allowances are included in the income figures. Where both husband and wife were wage-earners, their incomes have been added together. On the other hand, incomes of the children themselves have not been taken into account. Finally, information regarding the parents' occupations has also been obtained.

TABLE 1

Average height and average weight, etc.

Age	Number	Height, cm		Weight, kg	
		$M \pm s_m$	s	$M \pm s_m$	s
9.5–10.5	8	146.4 ± 3.10	8.8	39.2 ± 3.31	9.4
10.5–11.5	65	147.6 ± 0.77	6.2	37.5 ± 0.78	6.3
11.5–12.5	97	151.2 ± 0.70	6.9	41.0 ± 0.74	7.3
12.5–13.5	105	156.7 ± 0.71	7.3	44.5 ± 0.73	7.5
13.5–14.5	132	164.2 ± 0.75	8.7	50.9 ± 0.74	8.5
14.5–15.5	117	170.0 ± 0.75	8.1	57.2 ± 0.80	8.7
15.5–16.5	119	173.7 ± 0.67	7.3	59.9 ± 0.87	9.5
16.5–17.5	77	178.3 ± 0.62	5.5	65.0 ± 0.90	7.9
17.5–18.5	83	179.7 ± 0.76	6.9	67.8 ± 1.00	9.1
18.5–19.5	55	178.1 ± 0.76	5.7	68.6 ± 0.96	7.1
19.5–20.5	13	179.7 ± 1.75	6.3	69.3 ± 2.1	7.8
Total	871				

Average height and average weight in different age groups, together with standard deviations and standard errors of the means, are recorded in Table 1. Owing to the limited extent of the material, it has not been considered suitable to account in detail for its distribution over age groups, income groups and social groups. In order to exploit the material in its entirety in the statistical treatment, the analysis of variance has been applied.

In the beginning, the series was divided into 9 income classes, which, however, have mostly been combined, in the course of treatment, in three income groups. The division of the material into income classes and groups is set out in Table 2.

TABLE 2

Distribution of material by income classes and groups.

Notation		Number	Average income	Range
Groups	Classes			
I	1–3	336	6,545	–8,999
II	4–6	410	12,533	9,000–17,999
III	7–9	125	25,631	18,000–
Total		871	11,959	

TABLE 3

Differences in height and weight between children from different income groups.

Income groups	Height, cm		Weight, kg	
	D_w	F	D_w	F
I – II	+ 0.88	2.79	– 0.43	0.54
I – III	– 1.51	3.60	– 0.83	0.82
II – III	– 0.63	0.70	– 0.46	0.29
I – (II + III)	– 1.02	4.05*	– 0.53	0.85
II – (I + III)	+ 0.48	0.94	– 0.19	0.11
III – (I + II)	+ 1.00	2.00	+ 0.62	0.60
(1–4) – (5–9)	– 1.08	4.34*	– 0.87	2.19

In Table 3, the results of calculations regarding differences in height and weight between children from different income groups are given. Since the number of individuals in different age groups and income groups varies, the differences have to be weighted with regard to the varying frequencies. The unbiassed mean difference, D_w, is thus obtained from the formula SwD/Sw, where D is the difference between the individual age groups in two income groups, $w = n_1 n_2/(n_1 + n_2)$ and S indicates summation. The variance of the weighted difference D_w is $(SwD)^2/Sw$. If this variance is divided by the variance within the age groups, i.e. the individual variance, the variance ratio F is obtained.

For the differences in weight, the variance ratio F in no case reaches the figure 3.84, which, with regard to the actual number of degrees of freedom, corresponds to $P = 0.05$. It has thus not been possible to demonstrate any significant differences in weight between boys from different income groups. As regards the differences in height, F is in the majority of cases lower than

TABLE 4

Correlation between height (1), weight (2), income (3) and age (4).

$r_{13} = -0.02$	$r_{13.4} = +0.09$
$r_{14} = +0.80$	$r_{14.3} = +0.81$
$r_{34} = -0.09$	$r_{34.1} = -0.13$
$r_{23} = -0.05$	$r_{23.4} = -0.04$
$r_{24} = +0.77$	$r_{24.3} = +0.77$

TABLE 5

Distribution of material by social classes, etc.

Social class of the boys	Number of boys	Average income of the parents or guardians
Parents or guardians		
A. Employers	144	15,119
B. Civil servants and other employees . .	481	13,201
C. Workers	177	8,458
D. Pensioners	4	10,450
E. Woman guardians (widows, divorcees etc.)	65	5,394
Total	871	11,959

3.84, and never reaches 6.64, which corresponds to $P = 0.01$. In two cases, however, it exceeds 3.84, namely when the lowest income group is compared with the remaining groups ($F = 4.05$), and when the lowest four income classes are compared with the five higher ($F = 4.34$).

In a further effort to examine whether any relation exists between family income and the height and the weight of the boys at different ages, the correlation between height (1), weight (2), income (3), and age (4) has been computed from the ungrouped individual cases. Table 4 shows that, at a constant age, the correlation between height and income, or between weight and income ($r_{13.4}$ and $r_{23.4}$), is practically nil.

Since it was possible that at least in the lowest income group, income group 1, some connection could be found between height and income or between weight and income, the corresponding correlations have also been calculated within the groups. In no case could any significant correlation be found.

Finally, we have investigated whether any differences can be demonstrated in the heights or weights of boys from different social groups. The classification in social groups appears from Table 5, and the differences in height and weight have been tested in exactly the same way as in the case of income groups. The result can be seen in Table 6.

It is easily seen that the boys from group B, civil servants and other employees, are taller than boys from all other groups, and that the difference between group B and group C, workers, is very significant. For $P = 0.00$ we have $F = 10.8$, with the number of degrees of freedom occurring here. An attempt has also been made to find some correlation between income and height, or between income and weight, within the age groups of the differe

TABLE 6

Differences in height and weight between boys from different social classes.

Social classes	Height, cm		Weight, kg	
	D_w	F	D_w	F
A–B	−0.82	1.39	−0.32	0.16
A–C	+1.24	2.16	+0.93	1.05
A–E	+1.12	0.89	+0.43	0.11
B–C	+2.02	10.37**	+1.43	3.75
B–E	+1.82	3.60	+0.62	0.29
C–E	−0.04	0.00	+0.04	0.00

social classes, since some connection between income and social class undoubtedly exists. But it was found that all correlation coefficients except one were numerically less than 0.1. However, in group C, workers, the correlation between income and weight was 0.23, which implies some slight significance (t 3.02). Since it has been shown earlier that height is a more accurate measure than weight for changes in growth, and since no connection between weight and income has been arrived at from the material as a whole, this figure should be considered as accidental.

Discussion

The height and weight of Swedish school children were investigated by A. KEY in 1883. It should be noted that this investigation was one of the earliest made not only in Sweden, but throughout the world. KEY also compared the height and weight of children in elementary and secondary schools. Some of his results are summarized in Table 7.

KEY comments as follows: "The results of the comparison are thus completely in accordance with those reached in other quarters, and very clearly demonstrate the great influence which living conditions exercise on the growth and development of children. It should be unnecessary to recall that our investigations apply only to Stockholm elementary schools; that these children belong to the poorer classes, and in general live in worse domestic conditions than secondary school children, can certainly not be disputed. We cannot make any comparison with conditions in the country in Sweden, nor can we ascertain what part heredity may play in the less pronounced development of the poorer children."

TABLE 7

Comparison between the height and weight of boys in elementary and secondary schools according to KEY, 1883.

Age	Secondary schools			Elementary schools			Difference	
	Number	Height cm	Weight kg	Number	Height cm	Weight kg	Height cm	Weight kg
7	31	116	20.5	25	116	21.8	0	−1.3
8	87	121	22.8	175	117	22.5	+4	+0.3
9	109	126	26.2	197	122	25.8	+4	+0.4
10	77	131	29.3	316	125	26.3	+6	+3.0
11	693	133	30.3	353	129	28.7	+4	+1.6
12	1286	136	32.2	357	134	33.6	+2	−1.4
13	1737	140	34.5	276	137	33.0	+3	+1.5
14	2096	144	37.6	151	142	36.0	+2	+1.6
15	2076	149	42.3	42	144	37.0	+5	+5.3
16	1848	156	46.8	9	152	44.3	+4	+2.5

In order to obtain a more clear-cut comparison of KEY's results with those of later investigations, it would be of value to have an estimate of the statistical significance of the differences demonstrated by KEY between elementary and secondary school boys. In KEY's study, the highest and the lowest existing height and weight within each age group were recorded. With a knowledge of the range and the size of the groups, the standard deviations can be estimated with the help of a table published by TIPPETT. In Table 8, the standard deviations, s, thus calculated, are presented. These are compared with the estimates of s which are obtained if the standard deviations derived from an investigation of the height and weight of Swedish schoolboys carried out by BROMAN *et al.* in 1938 are applied to KEY's material. As can be seen, they are in fairly good agreement. The standard deviations in KEY's investigation are practically the same as in present-day investigations. Thus, in this respect, no changes have taken place. In the following comparisons, the standard deviations calculated on the basis of the figures published by BROMAN *et al.* are applied, since the calculation of dispersions from the range is more uncertain.

Table 9 shows the weighted differences in height and weight between boys in different types of schools along with the corresponding variance ratios. The variances were weighted according to the procedure outlined above. In both cases the variance ratios are considerably higher than 10.8, which is the level required for a significance of $P = 0.001$ with the number of degrees

TABLE 8

Calculated standard deviations in KEY's investigation, 1883: (*a*) on the basis of the range, (*b*) on the basis of figures from BROMAN *et al.*

Type of school	*s*, calculated from the range	*s*, calculated from BROMAN's figures, 1940
Secondary schools, height . . .	9.53	7.72
,, ,, weight . . .	8.84	7.70
Elementary ,, height . . .	6.58	6.53
,, ,, weight . . .	4.27	5.39

of freedom occurring here. It may, however, be pointed out that the variance ratios for height are considerably higher than those for weight.

During nearly 70 years which have passed since KEY's famous investigation, similar more or less extensive examinations have been carried out on different occasions in Sweden. Of these, only the study by BROMAN *et al.* in 1938 need be mentioned. In a comparison between boys from elementary and secondary schools whom these authors describe as boys from different social classes, a height difference of about 3 cm was shown. No difference in weight could be demonstrated. This circumstance was considered to be connected with the fact that the higher classes possibly represent comparatively more isolated groups, for different conditions of environment should have caused differences in weight as well. From a comparison with KEY's data, it was found that boys are now considerably taller and heavier at the same age. The difference in height was most strongly marked in the 12–13 age group, where it amounted to 11–13 cm. After this age, the difference decreased, and, in boys of 21, was approximately 5 cm. Similar conditions were also found in the weight of the boys. The authors related this to the fact

TABLE 9

Calculated values of weighted differences in height and weight between boys in secondary and elementary schools, together with the variance Ratios. KEY's investigation.

	D_w	F
Height, cm	3.15	198.1***
Weight, kg	0.89	15.9***

TABLE 10

Average height and weight of corresponding groups of secondary school bo from the age of 10.5–20.5 years at different periods of time.

Age	Number	Height, cm			Weight, kg		
		1883	1938	1950	1883	1938	1950
10.5 20.5	871	152.1	163.6	166.4	42.7	52.3	54.2

that better living conditions foster a faster growth, but that the final stat is decided by hereditary factors. Hereditary factors were also held partiall responsible for the difference at adult age, caused by the breaking up of isolated groups through industrialization, better communications and migra tion to urban communities. This process results in an increase of heterozy goty and if genes for greater height are dominant, an increase in height must ensue.

Some comparisons between KEY's, BROMAN's and the present investiga tion will now be presented (Table 10). For this purpose, the material from the three investigations has been collected in groups equivalent in age distribu tion. Since KEY's investigation was carried out with clothes, weight has been revised accordingly. The average weight of clothes is stated by KEY, quoting QUETELET and KOTELMANN, to be about one-twentieth of the weigh of the body. The calculated average figure for weight in the group selected from KEY's material has therefore been multiplied by 0.95, before the figure was included in Table 10.

The increase in height during the 67 years from 1883 until 1950 which the comparison covers, thus represents 14.3 cm, corresponding to 0.21 cm per year. From existing information regarding the measurements of conscripts, it is evident that length of body has increased from 169 cm in 1887–90 to 175 cm in 1946, which means an increase of only 0.116 cm per year. It must be pointed out here that these measurements embrace conscripts from the whole country, while the school investigations are limited to Stockholm. It is clear, however, that the adult height has increased considerably less than that of the growing generation. The annual increase in height of boys during the period 1883–1938 amounted to 0.21 cm, whereas the corresponding increase during the period 1938–1950 was 0.23 cm. There is thus no reason to assume that their increase in height is diminishing.

Increase in weight during the period of growth was 174 g per year during the period 1883–1938 and 166 g per year during the period 1938–1950. He

again, the differences are insignificant. It should be of some interest to compare changes in weight and height in relation to each other. The quotient between weight in kg and height in decimetres was 2.80, 3.29, and 3.26 in the three cases under discussion. A clearer conception is perhaps given by ROHRER's index, which is $100 \times$ weight/(height)^3. The index figures are 1.21, 1.19 and 1.18, a very slight difference, which might indicate a slight tendency towards less weight in relation to height.

As was mentioned above, BROMAN *et al.* also studied the differences in height and weight between boys in elementary and secondary schools. The comparison, however, only covers the ages of 10–15 years. As regards height, it was found that $D_w = 3.75$ cm and $F = 60.7$; as regards weight, $D_w = 1.78$ kg, and $F = 14.1$. In both cases P is < 0.001. It may be pointed out that the differences in weight are also here less marked than the differences in height. For reasons touched upon above, the authors consider that the differences demonstrated are less dependent on conditions of nutrition than upon other factors, most probably hereditary. No analysis of economic conditions is to be found in either KEY's or BROMAN's investigations.

The standard of living in Sweden has improved considerably, particularly since the time of KEY's investigation, but also since that of BROMAN's, while a significant levelling of the economic conditions of the different groups of society has simultaneously taken place. The public educational system also has passed through a substantial development. The pupils of the secondary schools are nowadays largely recruited from the elementary schools; in the former children from all classes of society are now to be found. It has therefore been possible, within one and the same secondary school, to compare the physical development of the children with the economic conditions and social position of the home. Economic developments have certainly brought with them a levelling of nutritional standards in different homes. Moreover, the schools have for several years provided free meals for all children who want them, and the majority take advantage of this facility.

In the investigation herein reported, no such differences in weight were found as might be due to the economic circumstances of the family. A correlation between height and income cannot be completely excluded, but if it really exists, it is much smaller than was found by earlier investigators. On the other hand, definite differences regarding height have been demonstrated between the different social classes. Hereditary factors may possibly be involved. We know, however, both from experience of human beings and from experiments with animals, that physical development is intimately connected with conditions of nutrition in a wide sense. The quantity of food as well as its nutritional quality are not only related to income but also to the way in which the income is spent, this being particularly manifest

TABLE 11

Differences in height and weight between boys of 11–14 years in Stockholm and Malmö, according to BROMAN *et al.*

	Height, cm		Weight, kg	
	D_w	F	D_w	F
Secondary vs. Elementary schools				
Stockholm	+ 3.00	31.14***	+ 1.03	3.86**
Malmö	+ 4.59	54.62***	+ 3.67	35.55***
Stockholm vs. Malmö				
Elementary schools	+ 3.52	44.37***	+ 3.02	34.54***
Secondary schools	+ 2.28	8.43**	+ 0.67	1.23

in Sweden, as here income is well in excess of the subsistence minimum. A closer analysis of the credit sides of the individual family budgets would certainly provide much of interest, as would a detailed investigation of the diet in individual cases. These problems could not be considered in this investigation. It would be of great value if it were possible in the future to study the height, weight and general state of nutrition of the members of the families in connection with general investigations of the cost of living.

The influence of social origin is certainly extremely complex. Apart from possibly significant hereditary dissimilarities, it is certainly conceivable that general differences in upbringing and environment may create different qualifications for adopting new ideas of personal hygiene and an increased receptivity to what may be advantageous for the health of the children.

In this connection, it is worth while pointing out that BROMAN *et al.* have shown the existence of certain differences between height and weight in different parts of the country. In 1934, the highest average height of conscripts, 174 cm, was registered in the military district of Gotland, and the lowest, 171 cm, in that of Upper Norrland. Here again it appears that the differences are more pronounced during adolescence. As indicated in greater detail in Table 11, BROMAN's investigations show an obvious difference in height between schoolboys in Stockholm and Malmö, both in elementary and secondary schools. As regards weight, the difference in the elementary schools was to the advantage of the Stockholm boys, but such was not the case in the secondary schools. The differences between the boys in secondary and elementary schools were noticeable, and greater in Malmö than in Stockholm. This comparison was, however, confined to the age period 11–14 years.

It is clear that it would be highly desirable to obtain further experimental evidence enabling us to form a more precise estimate of local and other dissimilarities in the physical development of growing youth. It would be advantageous in such an investigation to take into consideration the income and social position of the family and the distribution of the income into items of expenditure. Such an investigation would be even more valuable, could it be combined with an enquiry into the general standard of hygiene of the home and the nutritional standards of the children. But even a more limited scope could be of value. It may here be recalled that most of the earlier investigations have been made in towns; which was natural owing to practical experimental considerations. Through a suitable choice of schools, it would, however, be possible to subdivide the material, according to whether the children had grown up in urban areas or in rural districts. It is to be hoped that it will be possible to carry out such investigations in the near future.

Summary

During the past 70 years, schoolboys in Stockholm have increased about 15 cm in height and about 12 kg in weight, while the increase in height of the adult population is scarcely half as great. No relation between family income and the weight of the boys could be shown. A slight connection between the income and increase in height cannot be ruled out. A significant correlation is to be found between height and social class. The probable reasons for this are discussed. Some relevant research problems, deemed to be of a particular interest, are briefly outlined.

Taille et Poids des écoliers d'une école secondaire de Stockholm en 1950, et comparaison avec des résultats antérieurs.

Au cours des 70 dernières années, la taille et le poids des écoliers de Stockholm ont augmenté respectivement de 15 cm et de 12 kg, alors que pendant ce temps, la taille de la population adulte augmentait d'à peine la moitié. On n'a pu établir aucun rapport entre le revenu de la famille et le poids de l'enfant. Une discrète relation entre revenu familial, et augmentation de taille ne peut pas être éliminée. Il existe un rapport significatif entre la taille et la classe sociale. Les raisons probables en sont discutées. Les recherches ultérieures, destinées à éclaircir les problèmes en suspens, sont brièvement esquissées.

Grösse und Gewicht von Schulknaben einer Stockholmer Volksschule, 1950, und ein Vergleich mit einigen früheren Untersuchungen.

In den letzten 70 Jahren hat die Grösse der Stockholmer Schulknaben um etwa 15 cm und das Gewicht um etwa 12 kg zugenommen, während die Grössenzunahme bei der erwachsenen Bevölkerung kaum halb so viel beträgt. Es konnte keine Beziehung zwischen dem Familieneinkommen und dem Gewicht der Knaben gezeigt werden. Die geringe Beziehung zwischen dem Einkommen und der Grössenzunahme kann

nicht ausgeschlossen werden. Eine signifikante Beziehung besteht zwischen Grös- und sozialer Klassenschicht. Die wahrscheinlichen Ursachen dafür wurden diskutier Einige anwendbare Forschungsprobleme von Interesse werden kurz umrissen.

Estatura y peso de los niños en una escuela secundaria en Estocolmo. Estudio compar tivo con investigaciones anteriores.

Durante los últimos 70 años, la estatura y el peso medios de los niños en ed escolar en Estocolmo ha aumentado aproximadamente en 15 cms y 12 kgs., respect vamente, mientras que el aumento en la estatura media de la población adulta alcanz escasamente a la mitad de esta cifra. Aunque no pudo demonstrarse una categóric relación entre la estatura de los niños y el monto total de los ingresos familiares, un cierta conexión entre estos dos factores no puede descartarse del todo. Se discuten la causas probables de una correlación significativa entre estatura y condición social, y se esquematizan brevemente algunos problemas cuya investigación se considera de interés particular.

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Selective Filtration of Syphilitic Reagins through the Placenta

by ELSE VOGT

It is known that antibodies can pass from mother to foetus across the placenta, and it is usually assumed that the complement fixing antibodies pass the placental barrier more readily than do the precipitins.

Syphilitic reagins behave like other antibodies. If a mother has been cured of the syphilitic infection, but remains seropositive, syphilitic reagins may pass from her blood to that of her infant, who will be free of disease even though carrying reagins passively acquired from the mother. The titre of such passively acquired syphilitic reagins will be lower in the serum of the infant than in that of the mother; in the course of a few weeks or months after birth the reagin titre in the infant will fall until it becomes undetectable (Wiener).

We have studied the serological reactions of 107 newborn children born to mothers who where seropositive during the late stages of pregnancy. We found that the Meinicke clarification reaction (MKR) is always negative at birth, even in cases where the infant has been infected. In two cases where the infant had been infected, its MKR became positive at the age of 2–3 months. The precipitation reaction of Wadsworth and Brown (WBR) was always positive in the serum of an infant if it was positive in the serum of its mother, and the two sera differ little in the strength of their reaction.

Material and Methods

The blood samples were collected between March 1947 and April 1953, and tested by the complement fixation test of Bordet-Wassermann (WR), the precipitation reaction of Wadsworth and Brown (WBR) and the clarification reaction of Meinicke (MKR). Before January 1, 1950, a crude cholesterolised beefheart antigen was used for the WR, since then a standardised cardiolipin-lecithin cholesterol antigen (Pangborn). All sera showing a positive WR, and since July 1949 those showing a positive MKR, were titrated and scored, complete inhibition of haemolysis in the WR and complete clarification in the MKR being given the score 4, and lesser degrees the scores 3, 2, or 1. The score of every tube in a titration series was added to give a figure for the titre of the serum.

In the WBR and the MKR before July 1949, titrations were not performed, varying degrees of positiveness being indicated by the symbols +, + +, + + +.

Eighty-nine of the blood samples from the pregnant women were taken at the time of delivery or during the last month of pregnancy, 10 during the last 3 months and 7 earlier in pregnancy.

One hundred and two of the samples from the infants were taken at birth or during the first week, the other 5 during the first month of life.

Table 1 shows the results of MKR and WR on the serum from 106 pregnant women and their 107 newborn infants. (WBR is not recorded in the table because the reaction was positive in all the cases in serum from both mother and offspring and varied little in degrees of positivity from mother to infant.)

It is shown in the table that all the 107 infants have negative MKR even where the serum of the mother has a reagin titre of 20–30.

With the cardiolipin antigen about $\frac{3}{4}$ of the infants with WR positive mothers have positive WR. The less sensitive crude antigen, used on the first 39 cases, gave a positive WR in about $\frac{1}{3}$ of the infants. The serum reagin titre of the infant was in no case higher than that of the mother. By retesting 1–3 months after birth, 27 of the untreated infants were seronegative. (The others were either treated or not tested.) This indicates that the serum reagins of the infants were passively acquired.

Fig. 1 shows the average reagin titre obtained with WR and MKR on the serum from mother and child in 64 cases, using cardiolipin antigen. The average serum reagin titres of the mothers were practically the same with WR and MKR, contrary to the findings in the children.

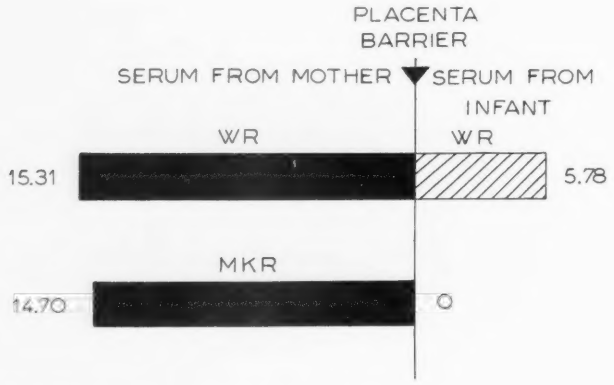

Fig. 1. Average reagin titres with Meinicke and Wassermann reactions in 64 sera from mothers and their newborn infants.

Table 1

Results of Meinicke and Wassermann reactions on the serum from 107 newborn infants and their 106 seropositive mothers (No. 57: twins).

Year	No.	Meinicke		Wassermann		Year	No.	Meinicke		Wassermann	
		Mother	Infant	Mother	Infant			Mother	Infant	Mother	Infant
1947	1	+ + +	–	16	–	1950	54	15	–	14	8
	2	+ + +	–	14	7		55	11	–	12	9
	3	+ + +	–	21	–		56	9	–	16	15
	4	– + +	–	5	–		57	21	–	20	+
	5	+ + +	–	12	5		58	14	–	16	–
	6	+ + +	–	9	3		59	9	–	16	–
	7	+ + +	–	16	7		60	22	–	22	–
	8	+ + +	–	13	–		61	16	–	19	9
	9	+ + +	–	5	4		62	10	–	12	4
	10	+ + +	–	9	6		63	18	–	13	8
	11	+ + +	–	15	3						
						1951	64	24	–	20	10
1948	12	+	–	–	–		65	26	–	16	12
	13	+ + +	–	13	–		66	6	–	11	8
	14	+ + +	–	14	0		67	15	–	14	12
	15	+ + +	–	11	4		68	20	–	23	8
	16	+ + +	–	11	–		69	27	–	32	9
	17	+ +	–	10	–		70	1	–	6	–
	18	+ + +	–	16	0		71	9	–	21	5
	19	+	–	2	–		72	13	–	20	5
	20	+ + +	–	29	–		73	20	–	15	11
	21	+ + +	–	6	–		74	11	–	5	–
	22	+ + +	–	8	2		75	10	–	12	4
	23	+	–	2	–		76	6	–	8	3
	24	+ + +	–	19	6		77	20	–	23	11
	25	+ + +	–	16	–		78	12	–	16	–
							79	8	–	11	8
1949	26	+ + +	–	8	4		80	12	–	12	–
	27	+ – +	–	9	–		81	11	–	12	2
	28	+	–	5	–		82	12	–	15	6
	29	+ + +	–	15	–						
	30	+ + +	–	15	5	1952	83	16	–	22	1
	31	+	–	–	–		84	16	–	22	11
	32	+ + +	–	23	–		85	27	–	29	12
	33	+ + +	–	9	–		86	12	–	16	7
	34	+ +	–	1	–		87	20	–	19	10
	35	18	–	19	–		88	11	–	12	9
	36	14	–	6	1		89	11	–	13	4
	37	15	–	6	–		90	13	–	16	–
	38	20	–	9	–		91	20	–	22	6
	39	1	–	4	–		92	17	–	13	7
							93	22	–	21	15
1950	40	4	–	4	3		94	26	–	26	9
	41	10	–	11	4		95	6	–	12	–
	42	17	–	13	8		96	17	–	18	8
	43	14	–	8	4		97	9	–	6	4
	44	28	–	20	6		98	20	–	16	13
	45	9	–	14	7		99	11	–	3	3
	46	20	–	20	13						
	47	17	–	14	–	1953	100	10	–	10	–
	48	4	–	7	0		101	16	–	13	7
	49	3	–	–	–		102	19	–	17	9
	50	14	–	12	–		103	28	–	23	4
	51	20	–	23	7		104	10	–	16	–
	52	1	–	5	–		105	9	–	8	5
	53	20	–	17	–		106	14	–	14	7

Discussion

Why should the MKR be negative in newborn children to whom syphilitic reagin has been passively transferred, when the WBR is always, and the WR usually, positive? The MKR is not less sensitive than the other reactions because in the same patient the titres of MKR and WR are almost equal. There is no evidence of a factor in the cord blood which inhibits the MKR: serum from an infant born to a strongly positive mother remains negative even when diluted with serum from a seronegative adult.

It seems probable that the MKR on the one hand, and the WR and WBR on the other, detect different types of antibody, and these differ in their capacity to pass the placenta, which bars that detected by the MKR and readily passes those detected by WR and WBR.

Observations on some of these infants suggest that the foetus *in utero* is quite unable to manufacture syphilitic reagins. Infant No. 3 had clinical signs of congenital syphilis; tests 2 months after birth showed a strongly positive MKR and WBR + + + while the WR, titre 24, was higher than that of the mother at delivery.

Infant No. 11 had *osteochondritis luetica* at birth. The syphilis of the mother was detected at the time of delivery and no treatment had been given during pregnancy. The child was treated with penicillin and trepinal (= spirocid) and the signs of *osteochondritis* disappeared.

Infant No. 15 had snuffles and rhagades about the mouth at birth. The mother had been treated from the end of the 8th month of pregnancy. Spirocid treatment of the infant brought the sero-reactions to negative.

Infant No. 33 with only a weak positive WBR at birth, showed after 3 months of life MKR 36, WR 28, WBR + + + +, reagin titres much higher than those in the serum of the mother at the time of delivery.

It would appear that the serum reagins in these syphilitic infants at birth were not formed by the infant, but merely due to the placental transfer of reagins from their syphilitic mothers.

It may be objected, however, that these infants, contrary to the clinical indications, were infected so close to term that they could not have had time to form detectable antibodies.

Conclusion

Meinicke's clarification reaction is not suitable for the detection of syphilitic reagins in the serum from newborn infants, because the reaction is always negative.

Summary

Selective filtration of syphilitic reagins through the placenta is studied. Three serologic tests for syphilis performed on the serum from 107 newborn infants are compared with the same tests on the serum from their mothers prior to delivery. Meinicke's clarification reaction (MKR) was negative in the serum from all 107 infants, even where the serum reagin titre of the mother was high at the time of delivery.

and the other tests were positive in the serum of the infant. It is concluded that MKR is not suitable for the detection of syphilitic reagins in the serum from newborn infants, because the reaction is always negative.

La filtration sélective des réagines syphilitiques à travers le placenta.

L'auteur étudie la filtration sélective des réagines syphilitiques à travers le placenta. Trois réactions sérologiques vis à vis de la syphilis ont été éssayées sur le sérum de 107 enfants nouveaux-nés, et ont été comparées avec les mêmes réactions faites sur le sérum de leur mère, antérieurement à l'accouchement. La réaction de clarification de Meinicke a été négative dans le sérum de tous les 107 enfants, même si le titre des réagines du sang de la mère était élevé au moment de l'accouchement, et que les autres réactions étaient positives dans le sang de l'enfant. La réaction de clarification de Meinicke n'est pas valable pour la détection des réagines syphilitiques dans le serum des nouveaux-nés, car elle est toujours négative.

Die selektive Filtration von syphilitischen Reaginen durch die Plazenta.

Die selektive Filtration von syphilitischen Reaginen durch die Plazenta wurde studiert. Drei syphilitische Serumreaktionen, die mit dem Serum von 107 Neugeborenen durchgeführt wurden, werden mit denselben bei den Müttern vor der Entbindung ausgeführten Serumreaktionen verglichen. Meinickes Klärungsreaktion (MKR) war bei allen 107 Neugeborenen negativ, auch wenn der Serum-Reagin-Titer der Mütter zur Zeit der Entbindung hoch war und die anderen Serumreaktionen des Kindes positiv waren. Die MKR ist nicht für den Nachweis syphilitischer Reagine im Serum Neugeborener anwendbar, da die Reaktion immer negativ ist.

Filtración selectiva de reaginas sifilíticas a través de la placenta.

Se investiga la existencia de filtración transplacentaria selectiva de reaginas sifilíticas. Se efectúan tres tests serológicos de la sífilis con el suero de 107 niños recién nacidos, y sus resultados son comparados con idénticos tests serológicos practicados en la madre antes del parto. La reacción de Meinicke (MKR) fué negativa en el suero de todos los 107 recién nacidos, aún cuando el título de reaginas en el suero de la madre era alto en el momento del parto, y los demás tests serológicos eran positivos en el niño. Se concluye que la MKR no es apropiada para detectar reaginas sifilíticas en el suero de niños recién nacidos, porque la reacción es siempre negativa.

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We should like to express our thanks to Dr George Discombe, Central Middlesex Hospital, London, who has read the manuscript and made many valuable suggestions.

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On Tuberculosis of the Bones and Joints of BCG Vaccinated Children

by ALF BACKMAN and ERIC IVAR WALLGREN

Since the introduction of BCG vaccination in Finland in 1941 over a million persons have been vaccinated. According to S. SAVONEN, the results in this country have been favourable.

An objective evaluation of the results of BCG vaccination requires the careful checking of all cases of tuberculous disease appearing after BCG vaccination. This is necessary to ensure that vaccination errors or incorrect diagnosis do not detract from the positive aspects of vaccination.

The majority of the cases which seem to have contracted tuberculous disease in spite of BCG vaccination reveal on a closer analysis that some mistake has been made in connection with the vaccination or in the assessment of the cases. Usually cases of post-vaccination tuberculosis are primary tuberculosis, erythema nodosum, pleurisy, early post-primary pulmonary tuberculosis and meningitis. So far very little is known whether benign late forms of tuberculosis, such as tuberculosis of the bones and joints, occur after BCG vaccination, and whether this vaccination provides protection against them.

DAHLSTRÖM & DIFS include in their report one case of tuberculous spondylitis and one of tuberculous gonitis without giving any detailed description of the cases. DAHLSTRÖM, in a later review of the same material, mentions 8 cases of tuberculosis of the bones and joints in BCG vaccinated subjects, though again without a detailed analysis.

SCHEEL reports 9 cases of tuberculous disease in BCG vaccinated subjects, including one case of tuberculous coxitis. The cases are not described in detail here either, but SCHEEL mentions by way of summary that the cases occurred 7–62 months after BCG vaccination and that the vaccination had been carried out between 1927 and 1931 when small doses of an unstandardised vaccine were employed. This made the result of the vaccination uncertain.

As we have found in the available literature only 9 cases of tuberculosis of the bones and joints in BCG vaccinated subjects we consider that it may

be of interest to report an investigation on children who were considered BCG vaccinated but nevertheless contracted tuberculosis of the bones and joints.

Material

The series consists of 40 cases studied between 1947–52. The age of the children on admission varied between 1 and 11 years. The average age was 4. The number of cases has increased during the latter years, probably due to the fact that relatively few vaccinations were effected before 1948, the year when mass vaccination was introduced. Eleven children suffered from gonitis, 11 from coxitis, and 7 from spondylitis; in a few cases there were other localisations. Three cases had more than one focus.

The total number of cases of tuberculosis of the bones and joints in the said hospitals during the same time was 727.

Results

For detailed examination the cases were classified into groups following in the main the schema suggested by USTVEDT for the assessment of BCG vaccinated cases of tuberculosis.

Group I. The patient has not been BCG vaccinated at all: 5 cases.

Group II. BCG vaccination had been performed in the pre-allergic phase of a virulent infection: 5 cases.

Group III. Virulent infection during the pre-allergic phase of BCG vaccination: 9 cases.

Group IV. Tuberculous patients have by mistake been BCG vaccinated: 2 cases.

Group V. Patients who have been BCG vaccinated and whose sensitivity to tuberculin after vaccination is unknown.

Two cases (1 and 2) of patients BCG vaccinated in the maternity hospital contracted tuberculous coxitis at the age of 4½ years. Data on their reactions to tuberculin are missing.

Group VI. Vaccination of a tuberculin-positive patient whose general condition was impaired due to another disease, and whose sensitivity to tuberculin had disappeared transiently.

Case 3. A girl of 8 was exposed to the risk of TB infection at home. Soon after having had measles she showed a negative reaction to the tuberculin test and was BCG vaccinated 4 days later. No tuberculin check was effected after vaccination. One year later she became ill with tub. art. cubiti; just before the onset of the disease the tuberculin reaction was positive.

Group VII. BCG vaccinated patients who have failed to develop a positive reaction to tuberculin.

One definite case belongs to this group.

Case 4. BCG vaccinated at birth. Six weeks later tuberculin-negative. At 8 months contracted a prolonged cough; at 2 years 3 months symptoms of tuberculous coxitis.

In addition, there are 9 uncertain cases which will be reported on later.

Group VIII. BCG vaccinated persons who have become tuberculin-positive but nevertheless contracted tuberculosis.

There are 6 unquestionably belonging to this group.

Case 5. BCG vaccinated at 6 years. Mantoux negative before vaccination, positive 3 months later. At 9 heavily exposed to the risk of infection for 8 months. At 10 years 8 months BCG scar showed signs of suppuration. Two months later symptoms of iridocyclitis and gonitis tub.

Case 6. BCG vaccinated at 7 years. Patch test negative before vaccination, positive after. Two years 2 months after BCG vaccination symptoms of caries costae tub. At the time of the onset of the disease the patient was exposed to the risk of TB infection.

Case 7. BCG vaccinated at birth. At 16 months tuberculin-positive. At 2 years 10 months symptoms of tuberculous gonitis. No source of infection could be traced.

Case 8. BCG vaccinated at birth. At 9 months tuberculin-positive. At 3 years 9 months contracted pleurisy; at 4 years 4 months symptoms of spina ventosa. The patient was heavily exposed to the risk of infection at home.

Case 9. BCG vaccinated at birth and subsequently showed positive patch test. At 3 years 10 months symptoms of spina ventosa. No source of infection could be traced.

This case could possibly be referred to Group V as nearly 4 years elapsed between vaccination and the onset of the disease.

Case 10. Vaccinated at 8 months; tuberculin-negative before vaccination, tuberculin-positive 3 months after it. Tuberculous gonitis 2 years 10 months after vaccination. No source of infection could be ascertained.

To the last two groups must be referred another 9 cases. We have been unable to decide in which of the groups they should be placed as they were not tested for tuberculin reactions after vaccination. One of these cases we consider deserving of a detailed description.

Case 11. BCG vaccinated at 9 years. Re-vaccinated 6 months later as tuberculin reaction has not become positive. Eighteen months later became ill with tuberculous gonitis; Trambusti then positive. No source of infection could be traced.

The remaining 8 cases in this group are all similar in nature. A feature common to all of them is that no tuberculin check was made after vaccination. In 4 cases the interval between BCG vaccination and onset of disease was 8–12 months, in 4 cases 20–36 months.

Discussion

On checking the material we found that in 5 cases no BCG vaccination was effected. In 17 out of the remaining 35 cases the BCG vaccination was not made *lege artis* (Groups II–VI). In Group II a heavy exposure to the risk of TB infection in the home just prior to the vaccination has been detected in all 5 cases; hence the children should have been isolated and re-tested; the vaccination was done too late. In Group III the 9 children have been exposed to the risk of TB immediately after vaccination; these patients should have been isolated after vaccination. In Group IV vaccination was made on an incorrect indication as the 2 patients showed symptoms of active tuberculosis at the time of vaccination. In Group V the negative tuberculin reaction has been misinterpreted. According to the literature a positive reaction to tuberculin can become transiently negative after measles. The measles from which the patient had recently suffered and the existing risk of exposure to TB at home should have been taken into consideration. Hence, in 17 out of 35 cases a simple error was made in deciding BCG vaccination. We have been unable to observe any detrimental influence in the form of activation or a "negative phase" in these cases, and like many other authors we consider that BCG vaccination has not been harmful. However, a more careful check is required to ensure that BCG vaccination is not blamed for such mistakes.

With the case of Group VII, too, we consider that a mistake was made since the patient was not re-vaccinated after a negative tuberculin test had indicated that the vaccination had not taken.

In the remaining 17 cases we have found that the patients were infected with virulent TB bacilli and contracted a tuberculous disease after a BCG vaccination which should have protected them. All these cases contracted the disease more than 6 months after the BCG vaccination. No protection can be counted on for the first 6–8 weeks after BCG vaccination and an interval of 4 months can be assumed between infection and the appearance of the symptoms in the bones and joints. Eleven of these cases were not tested for tuberculin reactions after vaccination, and therefore there is no evidence of their having attained a state allergic to tuberculin. It can also be thought that tuberculin-positivity may have disappeared.

Scheel (1935) reports that a BCG vaccinated person who has developed allergy to tuberculin may lose his tuberculin sensitivity as early as 6 months later. According to Scheel (1941) we cannot count on any protection from BCG after 4–5 years, unless human superinfection has maintained the allergy.

Wasz-Höckert and Donner (lecture at the meeting of *Finska Läkaresällskapet* 1953) indicate that 2½ years after vaccination one-third of the

vaccinated subjects cease to react to tuberculin. Following this opinion, we have referred two of the above-mentioned 11 incompletely checked cases where 4½ years had elapsed between the vaccination and onset of the disease to Group V. Another case with an interval of 2 years 4 months between vaccination and onset of disease could perhaps also be referred to this group. In the meantime these cases, as far as we have been able to check, have not been exposed to infection.

In 3 out of the 6 cases with a demonstrable positive allergy to tuberculin after vaccination (Group VIII) the interval between vaccination and the onset of disease was 3 years 10 months, 2 years 10 months, and 2 years 2 months, and no source of infection at home has been traceable. It is possible that reaction to tuberculin may have disappeared in any of these cases. One of these 6 cases (Case 5; Group VIII) developed, at the time of the virulent infection, a Koch's phenomenon in the BCG vaccination scar. This is unquestionable evidence of the patient's positive allergy to tuberculin at the time of the onset of disease. Of the most benign four cases of the material, i.e. 3 cases of spina ventosa and 1 of caries costae tub., 3 are included in these 6 cases vaccinated *lege artis*.

In order to show the period elapsing between vaccination and the development of the first symptoms of tuberculosis in the 17 cases infected after vaccination we have compiled the following table:

Onset of the disease occurred	
7–12 months after BCG	in 4 cases
13–18 » » »	» 1 case
19–24 » » »	» 2 cases
25–30 » » »	» 3 »
31–36 » » »	» 2 »
37–42 » » »	» 0 »
43–48 » » »	» 2 »
49–54 » » »	» 3 »

The time of the onset of the disease is therefore evenly distributed over a long period following the vaccination, which seems to contradict the existence of a "negative phase".

From the records and by the questionnaire, we have attempted to estimate the degree of exposure in the above 17 cases as strong in 2 cases; extra-domiciliary exposure, 2 cases; slight exposure, 2 cases; and no known exposure in 11 cases. Hence, a strong exposure to tuberculosis can be shown in a surprisingly low number of cases.

Summary

No harmful effect of BCG vaccination has been found in the present group of 17 cases of bone and joint tuberculosis occurring in adequately vaccinated subjects. In these cases the disease has taken a mild course; however, the number is too small to permit of any definite conclusions. In only 2 of the cases a strong exposure had occurred, in the others only a slight one, or exposure was not detected.

La tuberculose des os et articulations chez les enfants vaccinés par le B.C.G.

Dans un groupe de malades atteints de tuberculose osseuse ou articulaire, les auteurs ont relevé 17 cas, survenant après une vaccination correcte par le B.C.G. Aucun effet défavorable de la vaccination n'a été noté. Dans tous les cas, la maladie a été bénigne. Mais, le nombre est trop limité pour permettre des conclusions absolues. Dans deux cas, seulement, on a relevé un contage massif; un a été bénin, et les autres n'ont pu être déterminés.

Über Knochen- und Gelenktuberkulose bei BCG-vaccinierten Kindern.

Das Material besteht aus einer Gruppe von 17 Knochen- und Gelenktuberkulosen, die alle lege artis vacciniert worden waren, und bei denen keine schädliche Wirkung der BCG-Vaccination beobachtet werden konnte. In diesen Fällen hat die Erkrankung einen milden Verlauf gehabt, jedoch ist die Zahl zu klein, um endgültige Folgerungen ziehen zu können. Nur in 2 der Fälle war eine starke Exposition vorhanden gewesen, bei den übrigen Fällen konnte nur eine geringe oder gar keine Exposition nachgewiesen werden.

Tuberculosis ósteo-articular en niños vacunados con BCG.

En un grupo de 17 casos de TBC ósteo-articular en niños adecuadamente vacunados con BCG no se ha observado efecto nocivo de esta vacunación. En estos casos la enfermedad ha tenido una evolución benigna, pero su reducido número no permite extraer conclusiones definitivas. En solo 2 de los casos hubo antecedentes de exposición a contagio bacilar intenso; en los otros la exposición fué solo leve o no pudo detectarse.

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Aus dem Krankenhaus des Finnischen Roten Kreuzes, Vorstand: Professor Dr. med. Aarno Snellman, sowie der Kinderklinik der Universität Helsinki, Vorstand: Archiater Professor Dr. med. Arvo Ylppö.

Über die EEG-Befunde bei Enuresis

von YRJÖ TEMMES und ERKKI TOIVAKKA

Kennzeichnend für die Funktion des infantilen Zentralnervensystems ist ein geringer Grad der Differenzierung, demzufolge die auf neuronalem Wege als Impulse wirkenden Funktionssteuerungen sich über ausgedehnte periphere Gebiete ausbreiten und als sog. primitive Massenreflexe zum Ausdruck kommen. Bei Säuglingen kommt es in Verbindung mit der Erschlaffung des Blasensphinkters und dem zunehmenden Tonus der Wandmuskulatur auch zu Bewegungen oder einem spastisch betonten Spannungszustand in den Gliedmaßen und bisweilen im ganzen Körper. In den späteren Stadien der Entwicklung des neuronalen Gewebes trennen sich diese Funktionen. Andererseits, ist einmal der Sphinkter erschlafft, vollzieht sich die Miktion bis die Blase leer ist. Eine willkürliche Unterbrechung des Harnstrahles ist im Prinzip möglich, gelingt aber auch beim Erwachsenen nicht ganz ohne Mühe. Somit kann beim Kind schon eine ganz kurzfristige Störung in der Kontrolltätigkeit des ZNS zur Entleerung der Harnblase führen.

Nach GUNNARSON und MELIN treten insbesondere bei denjenigen Enuretikern, bei denen nach der Periode der physiologischen Unsauberkeit nicht eine kürzere oder längere Periode der Sauberkeit vorgekommen ist, in einer bedeutenden Zahl von Fällen pathologische Veränderungen in der hirnelektrischen Tätigkeit auf.

Das Vermögen zur Kontrolle der Blasenfunktion nach dem $2\frac{1}{2}$. bis 3. Lebensjahr kann infolge einer allgemeinen oder partiellen, kongenitalen oder erworbenen Entwicklungsstörung des ZNS fehlen oder seine Ausformung zum bedingten Reflex gehemmt sein. Erfahrungsgemäß kommen solche Entwicklungsstörungen oft als pathologische Veränderungen im EEG zum Vorschein.

In der EEG-Abteilung des Krankenhauses des Finnischen Roten Kreuzes wurden 43 größtenteils aus der Kinderklinik der Universität überwiesene Enuretiker untersucht, dazu im EEG-Laboratorium des Lapinlahti-Hospitals 11 Falle. In den meisten Fällen war die intellektuelle Entwicklung der Unter-

TABELLE 1

Alter und EEG-Befund.

Alter, J.	Anzahl Fälle	EEG:0	EEG:+
3–4	5	2	3
4–6	18	2	16
6–8	14	0	14
8–10	8	1	7
10–12	3	0	3
12–14	2	0	2
14–16	4	1	3
Gesamtanzahl	54	6	48

suchten bei der Prüfung als normal geschätzt worden, in zwei Fällen lag ein eindeutiger psychischer Defektzustand vor, in drei Fällen betrug der IQ (Terman-Merrill) etwa 80.

Bei 6 von den 54 Untersuchten waren die EEG-Befunde als normal zu beurteilen, in 48 Fällen als positiv, d.h. es kamen kontinuierliche oder paroxysmal auftretende Veränderungen in den Kurven vor. In der Tabelle 1 sind die EEG-Befunde und die Verteilung der Enuretiker hinsichtlich des Alters zusammengestellt.

Von den untersuchten Kindern waren 16 Mädchen und 38 Jungen.

Den klinischen Symptomen nach wurde das Material in drei Gruppen geordnet: 1. Enuresis als einziges Symptom in der Anamnese und während des Aufenthaltes im Krankenhaus, 2. das meist ausgeprägte Symptom Enuresis, dazu gelegentliche Anfälle, über die jedoch meistens kein hinreichend genauer Bescheid zu erhalten war, 3. Enuresis als wesentliches Symptom im Zusammenhang mit organischen Defekten des ZNS. Die Verteilung der EEG-Befunde auf diese drei Gruppen ist in der Tabelle 2 wiedergegeben.

Als epileptisch haben wir nur die Befunde beurteilt, die eindeutige spezifische Potentialschwankungen aufzuweisen haben. Solche Befunde sind in unserem Material bei 41 % vorhanden. Von manchen Autoren werden alle paroxysmal auftretenden Veränderungen der Hirnpotentiale als epileptisch gewertet, jedenfalls sind die paroxysmal ausgeprägten trägen Wellen der Ausdruck einer erhöhten Anfallsbereitschaft. Rechnet man die Gruppe der epileptischen Befunde und die der unspezifischen paroxysmalen Veränderungen zusammen, so ergibt sich in unserem Material eine Erhöhung der Anfallsbereitschaft von 68 % gegen 32 %, bei denen eine solche bei der EEG-Untersuchung nicht nachgewiesen werden konnte. Negative EEG-Befunde,

TABELLE 2

Klinische Gruppierung und EEG-Befund.

Klinische Gruppe	Anzahl Fälle	EEG: 0	EEG: unentschieden	EEG: paroxysmale Störungen	EEG: spezif. epileptische Störungen
Enuresis	39	5	8	13	13
Enuresis und Anfälle . .	13	1	2	1	9
Enuresis und Defekt (Gruppe 3)	2	0	2	0	0
Gesamtanzahl	54	6	12	14	22

d.h. solche, wo keine eindeutigen Veränderungen vorhanden waren, kamen im ganzen Material nur in 11% der Fälle vor. Dagegen gibt es paroxysmal ausgeprägte Dysrhythmien in einem Normalmaterial nur in 0,9% (GIBBS), während in 86% der EEG-Befund normal ist.

Aus den verfügbaren Krankenberichten geht nicht immer hervor, ob sich das Einnässen an die Periode der physiologischen Unsauberkeit anschließt oder ob das Kind nach einem sauberen Zeitraum aufs neue einzunässen begonnen hat. In dieser Hinsicht verteilt sich das vorliegende Material, nach den Krankenberichten geordnet, in der in Tabelle 3 angegebenen Weise.

In der Gruppe der persistierenden Einnässer ergaben sich epileptische EEG-Befunde bei 44%, eine erhöhte Anfallsbereitschaft bei insges. 74%. Bei den Enuretikern, die nach der physiologischen Unsauberkeit eine saubere Periode gehabt haben, sind die entsprechenden Werte 23% und 46%. Die epileptischen Potentiale und paroxysmalen Veränderungen im EEG sind demnach etwa zweimal so häufig bei den persistierenden Einnässern als bei denjenigen, bei denen eine saubere Periode zwischengeschaltet gewesen ist.

TABELLE 3

Persistierende Nässer, erneute Nässer und EEG-Befund.

Gruppe	Anzahl Fälle	EEG: 0	EEG: unentschieden	EEG: paroxysmale Störungen	EEG: spezif. epilept. Störungen
Persistierende Nässer . .	34	4	5	10	15
Erneute Nässer	13	2	5	3	3
Keine Angaben	7	0	2	1	4
Gesamtanzahl	54	6	12	14	22

Aus den oben mitgeteilten Befunden ergibt sich erstens, daß zwischen de Enuresis und einem pathologischen EEG-Befund eine statistisch belangvoll Korrelation besteht, und zweitens, daß speziell den Epilepsien oder de epilepsieverdächtig ausgeprägten Dysrhythmien nahezu 70% vom vorliegen den Material zufallen. Es ist demnach evident, daß das Nachlassen de koordinierten Kontrolltätigkeit der übergeordneten Zentren im ZNS un physiologisch fehlerhafte Funktionssteuerungen der unterstellten Zentre als eine wichtige und nicht ungewöhnliche Grundlage für den Eintritt eine Enuresis angenommen werden müssen. Die pathologischen EEG-Befunde schließen indes keineswegs die eventuelle Rolle anderer Leiden oder psy chischer Umstände aus. Obwohl es für die Hirnpathologie irrelevant ist, welche Milieufaktoren und seelischen Erlebnisse bei einem Enuretiker be merkbar sind, so hat man doch in Betracht zu ziehen, daß eine mangelhaft gesteuerte und durch Rückkopplung kontrollierte Funktion ein „locus mi noris resistentiae" ist und als solcher stets leichter Störungen unterliegt als eine stabil gelenkte Funktion.

Zusammenfassung

Bei 54 Enuretikern wurde eine EEG-Untersuchung gemacht. Dreizehn von den Kindern hatten früher „Anfälle" gehabt. In etwa 70% der Fälle wurden ausgeprägte paroxysmale oder epileptische Veränderungen gefunden. Nur in 11 Fällen war der EEG-Befund als normal zu beurteilen. Die Ergebnisse zeigen, daß Störungen der zerebralen Kontrolle einen wichtigen Faktor in der Pathogenese der Enuresis dar stellen.

L'EEG dans l'énurésie.

Les auteurs ont étudié l'EEG chez 54 enfants atteints d'énurésie, et ne présentant pas d'autre symptôme. 13 d'entre eux ont eu des convulsions. Dans 70% des cas, ils ont observé des dysrythmies paroxystiques non typiques, ou des potentiels épileptiques. Dans 11 cas, seulement, il n'y avait pas de modification de l'EEG. Il leur semble qu'on doit plutôt incriminer, comme étiologie, un trouble cérébral dans le contrôle de la vessie, qu'un déréglement ou un conflit de la personnalité.

Electroencephalographic findings in enuresis.

Fifty-four cases of children with enuresis as cardinal clinical sign were examined with the aid of EEG. Thirteen of them had previously suffered from convulsions. In about 70 per cent there were non-typical paroxysmal dysrhythmias or epileptic potentials. Only 11 cases had no changes in the EEG. It would seem that disturbances of cerebral origin in the control and communication of the bladder must be assigned a more important etiologic significance than many a disorder or conflict of personality.

Hallazgos electroencefalográficos en la enuresis.

Se estudió el EEG de 54 casos de niños cuyo signo clínico más evidente era la enuresis. En aproximadamente un 70% de los casos se observaron disrritmias paroxísticas

no típicas o potenciales epilépticos. En sólo 11 de los casos no se observaron alteraciones electroencefalográficas. Probablemente deba darse una mayor importancia diagnóstica a las alteraciones de origen cerebral en el control de la vejiga, que a alteraciones o conflictos de la personalidad.

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From the Pediatric Clinic of Athen's University
(Head: Prof. C. CHOREMIS)

The Effect of Hyaluronidase on the Moro Epidermal Tuberculin Reaction

by C. CHOREMIS, C. PAEDIATELIS, A. GAZOULIS and D. ZOUMBOULAKIS

McCLEAN and MORGAN reported rapid absorption of diphtheria antitoxin on the addition of testicular extracts. LONG, YAMANE, and PINCUS and ENZMANN found a substance in semen which was able to dissolve vitelline membrane, and similar observations were made by McCLEAN and ROWLANDS, who attributed this quality to the hyaluronidase.

The successful use of hyaluronidase has been reported in hydrocephalus (SCHWARTZMANN) and in chronic limb oedema (FERRERO). In infantile dehydration it has become indispensable because of its ability to accelerate absorption of large quantities of fluids administered subcutaneously (SCHWARTZMANN). DURAN and REYNALS found that it increased the intensity of the skin reaction in smallpox vaccination, and McCLEAN attributed this to the increased permeability of the skin. BERGQVIST observed that the use of hyaluronidase with BCG vaccination produced a stronger tuberculin reaction.

This study, based on the above-mentioned qualities, was made to determine whether hyaluronidase could affect the absorption of the tuberculin applied epidermally.

Material and Method

The material consisted of children treated in this clinic for various diseases and children recovering from tuberculosis in different sanatoria. The cases were divided into three groups:

Group A (control group). 81 cases. The usual Moro test was used (a mixture of 1 g of old tuberculin and 2 g of lanolin).

Group B. 392 cases. One g of hyaluronidase was added to the mixture used in the A group.

Group C. 316 cases. P.P.D. was used instead of old tuberculin in amounts of 25 units for each test.

Technique: A quantity of ointment the size of a small lentil was rubbed on a 3 cm area of skin in the subclavicular region, until it was completely absorbed. Contact

with clothing was avoided for half an hour, and the results were read after 6, 12, 24, and 48 hours. The reaction was considered positive when erythema and small papules or vesicles appeared at the site of application of the tuberculin.

Results and Comments

The results are summarized in Table 1. As can be seen from this table, the percentage of positive reactions with the Moro test in the group with positive Mantoux tests was 79 per cent in group A. In most cases (70.31 per cent) the reaction became positive after 48 hours. In group B the percentage of positive reactions was 81 per cent of those with positive Mantoux tests, and the time of appearance in the great majority of cases (53.11 per cent) was 12 hours. The positive reactions in group C were 98.8 per cent of positive Mantoux tests and the time of appearance was 12 hours in most of the cases (58.2 per cent).

The above results confirm the obvious accelerating effect of hyaluronidase on the appearance of tuberculin reaction.

The practical importance of this method should also be considered, since the result can be read after a shorter period of time. It would be of a practical interest to determine whether the hyaluronidase-tuberculin mixture is stable. This problem is already under study.

TABLE 1

Time	A		B		C	
	Old Tuberculin (Mantoux positive 81)		O. T. + hyaluronidase (Mantoux positive 392)		P.P.D. + hyaluronidase (Mantoux positive 316)	
Hours	Moro positive	%	Moro positive	%	Moro positive	%
6	1	1.56	74	23.19	94	30.13
12	3	4.68	170	53.11	181	58.2
18	2	3.00	61	19.12	24	7.69
24	13	20.31	6	1.78	9	2.88
48	45	70.31	8	2.5	4	1.28
Total	64	79	319	81.4	312	98.8

Summary

Admixture of hyaluronidase to Old Tuberculin and P.P.D. for percutaneous tests produced a stronger and more rapid reaction in tuberculin-positive children.

Effet de l'hyaluronidase sur la réaction épidermique de Moro à la tuberculine.

Un mélange d'hyaluronidase avec la vieille tuberculine et avec la P.P.D., utilisé en tests percutanés a réalisé chez des enfants positifs, une réaction plus intense et plus rapide.

Die Wirkung der Hyaluronidase auf Moros epidermale Tuberkulinreaktion.

Durch Zusatz von Hyaluronidase zu Alttuberkulin und P.P.D. kann man bei tuberkulinpositiven Kindern eine stärkere und schnellere Reaktion mit der perkutanen Probe erzielen.

El efecto de la hialuronidasa sobre la reacción epidérmica a la tuberculina de Moro.

La adición de hialuronidasa a «tuberculina vieja» y P.P.D. usados en pruebas percutáneas, produce reacciones más rápidas e intensas en niños tuberculino-positivos.

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From the Hospital for Contagious Diseases, Stockholm. (Chief: Justus Ström, M.D.)

Penicillin Treatment and Immunity to Scarlatina[1]

by JUSTUS STRÖM

Following our first attempts at penicillin treatment of scarlet fever in 1946, it was not long before it became evident that the number of second attacks was greater than had previously been the case. It was natural to relate this phenomenon to a deterioration in immunity due to the treatment. The same observation has been made by other authors (se References), but no systematic study of this important problem has been undertaken.

On account of the number of these second attacks, constituting the only essential drawback to penicillin treatment, I considered it extremely important to study the question closely. This I have now been doing for five years. Conditions in Stockholm have been particularly suitable, since hospitalization of scarlatina patients has been compulsory and there has only been one hospital for their reception.

In order to obtain comparative material from earlier years in which an epidemic occurred, it was necessary that the investigation should comprise the period 1938–51. Fig. 1 illustrates the conditions as regards the total number of scarlatina cases and desquamation cases, and the percentage of second attacks.

It is necessary to define first what is here meant by second attacks. In the second attacks, or relapses, which take place in hospital, "cross infections" play an important role. The period of hospitalization was as a rule six weeks. A survey of this material, however, shows that the stay in hospital was often longer and that many relapses occurred up to the third month. Consequently a limit of three months had to be set in order to eliminate the factor—the risk of infection in hospital—which would otherwise distinguish cases treated by penicillin from those untreated. In the following, therefore, I shall speak of *early* and *late second attacks*, the former being divided into two periods from 0–6 weeks and from 7 weeks to 3 months.

It is seen from Fig. 1 that the number of cases in Stockholm shows great variations from about 350 per year to 3,600 in the epidemics of 1939 and

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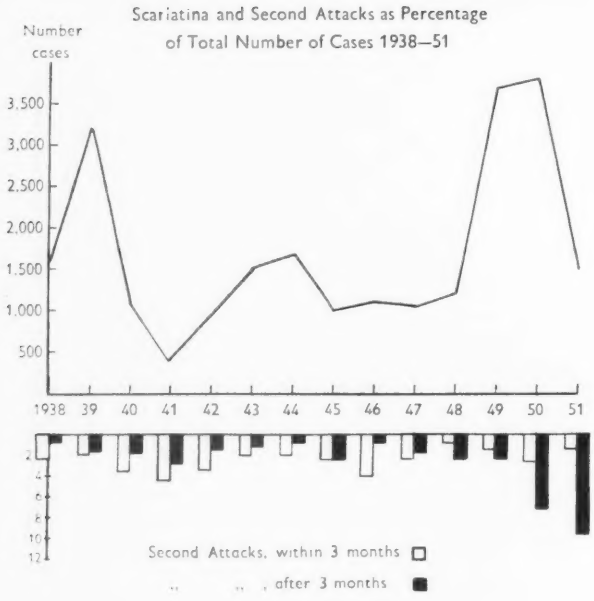

Fig. 1.

1949–50. When penicillin treatment was introduced on a large scale in 1947, the percentage of second attacks rose progressively, and this rise is due to the cases developing after 3 months. Thus in 1951 late second attacks constituted about 10 per cent of the total number of scarlatina cases.

The following investigation covers children between 0 and 14 years only. Above this age there now occurs only a small number of cases (about 5 per cent), but in the early 1940's the number was quite considerable (about 30 per cent) due to the presence of military barracks in Stockholm. First attacks only have been included, not second attacks. Since, moreover, only a small number of cases was treated with penicillin in 1946, and in 1947–49, in order to obtain comparative series, some were not treated with penicillin, the material has been tidied up in this respect as well, so that all cases from 1947 onwards have received penicillin treatment, but none before 1947. Table 1 shows second attacks in the reassorted series. Although the period of observation in the case of the untreated material was nearly four times as long, a manifest difference is evident in respect to the late second attacks. In cases of scarlet fever in acute stage they are 3.8 times, and of desquamation cases 2.4 times, as numerous as they were previous to the penicillin period.

This in itself shows that there must be a great difference in respect to the

TABLE 1

Second attacks of scarlatina before and after introduction of penicillin treatment at ages 0–14 years.

Period 1938–46: 7 362 cases scarlet fever not treated with penicillin
1 506 cases desquamation not treated with penicillin
(mean period observation 9 1/2 years)

Period 1947–51: 7 305 cases scarlet fever treated with penicillin
2 094 cases desquamation treated with penicillin
(mean period observation 2 1/2 years)

Second attacks	Scarlet fever acute stage		Desquamation	
	1938–46	1947–51	1938–46	1947–51
Within 6 weeks	191	106	62	5
%	2.6	1.5	4.1	0.2
6 w.–3 m.	36	77	9	3
%	0.5	1.1	0.6	0.1
Total	227	183	71	8
%	3.1	2.6	4.7	0.3
>3 months	87	327	10	35
%	1.2	4.5	0.7	1.7

interval between the first and second attacks in treated and untreated patients. This is illustrated in Fig. 2. All late second attacks from 1938 to 1946 are fairly evenly distributed up to 7 years from the first attack. For treated cases, on the other hand, from 1947–51, the maximum occurs in the 2nd–4th quarter of the first year and then falls rapidly to the third year after the primary attack.

An examination of the *age* on the occasion of the primary attack in children who were later reinfected with scarlatina, also shows that a marked change has taken place. Previously it was especially children who had had the disease at 3 years of age or less in whom second attacks developed. The incidence among penicillin-treated cases is equally high, about 5 per cent, from 2 to 7 years of age, and only falls gradually to about 3 per cent at 11–13 years of age. Thus, the risk of a second attack has risen considerably with the child's age. In the age groups 0–3, 4–8 and 9–14, the risk has increased twofold from 2.7 per cent to 5.0 per cent), fourfold (from 1.1 per cent to 4.7 per cent), and ninefold (from 0.3 per cent to 2.8 per cent), respectively.

For the purpose of obtaining as exact an expression as possible of the effect of penicillin, the comparison with earlier conditions should be made

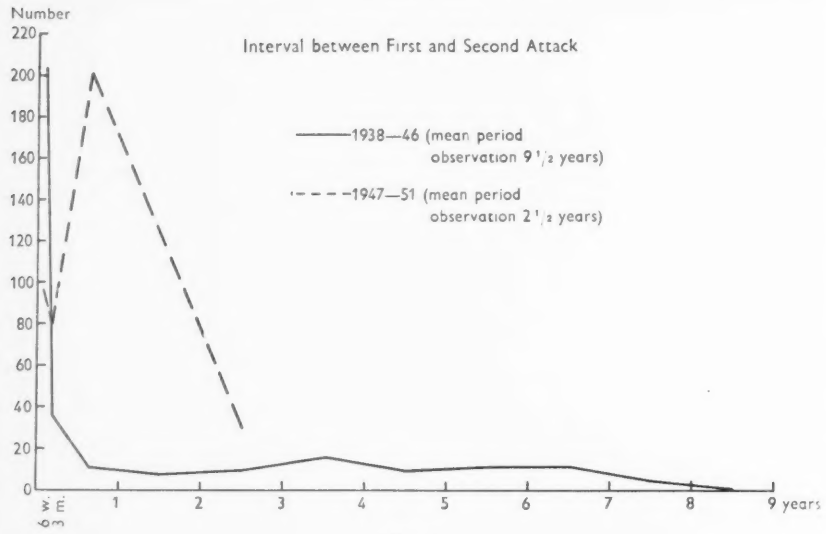

Fig. 2.

on reasonably similar assumptions. Second attacks of scarlatina will quite naturally be more numerous if an epidemic occurs with the consequent risk of new infection. For this reason a *comparison* has been made primarily *between the five-year periods 1938–42 and 1947–51, in each of which an epidemic took place*, and the years 1942–46 merely serve as an example of a five-year period without epidemic. Apart from similarity as regards epidemiologic conditions, however, the periods of observation should also be equal. The years 1947–51, in which the mean period of observation was 2½ years, must be taken as the norm, and the other periods have been adjusted to it. The result of this examination is presented in Table 2, which should be compared with Table 1.

The frequency of late second attacks during this shorter period of observation was 0.5 per cent for the epidemic period 1938–42. In comparison with the penicillin period 1947–51 the frequency of second attacks among treated cases was 4.5 per cent, i.e. nine times as great. As regards desquamation cases the corresponding figures are 0.3 and 1.7 per cent, the latter risk thus being 5.7 times as great.

These results should be fairly reliable, but greater exactitude can only be attained *by parallel series of treated and untreated cases*. Moreover in this way the results of different forms of treatment can be assessed.

Table 3 represents five different test periods. When the epidemic broke out in 1949, the comparative series had to be interrupted for a while, until

TABLE 2

Second attacks of scarlatina at ages 0–14 years for different five-year periods and equal mean time of observation ($2\,^1/_2$ years).

Second attacks	Scarlet fever acute stage			Desquamation		
	1938–42	1942–46	1947–51	1938–42	1942–46	1947–51
Within 6 w.	98	99	106	37	35	5
%	2.3	2.7	1.5	4.3	4.6	0.2
6 w.–3 m.	20	22	77	6	2	3
%	0.5	0.6	1.1	0.7	0.3	0.1
Total 0–3 m.	118	121	183	43	37	8
%	2.8	3.3	2.6	5.0	4.9	0.3
>3 months	21	5	327	3	–	35
%	0.5	0.1	4.5	0.3	–	1.7

the situation was brought under control and different methods of treatment could be introduced again. The variation in method and period of hospitalization is shown in the table. The following doses were given from 1–14 years of age:–

Test period	Dosage
a	5,000—15,000 IU × 8 (inj.)
b	20,000—60,000 IU × 7, then × 3, and 40,000—80,000 × 2 (inj.)
c, *d*, *e*	100,000—150,000 IU × 1 (pen.-proc.; inj.), 75,000—125,000 IU × 3 (pen.-proc., per os)

Time of treatment: until 3 neg. tests obtained on hemolytic streptococci, but not less than 6 days.

Concerning the *early second attacks* the following results were manifested. In the test periods *a* and *b*, a comparison was made between penicillin-treated and untreated cases. In the control series *Ka*, relapses within 6 week were no less than 20, or 8.8 per cent, while in the penicillin series *Pa* there were only 3, or 1.4 per cent. The conditions and time of hospitalization (6 weeks) were identical, and the result can only be interpreted as confirming that the risk of these relapses in hospital diminished considerably as a result of penicillin treatment. The control series *I-K* during the following period, however, shows that the same low frequency in the case of these early second attacks in hospital, could be obtained by isolation of the patients in private rooms, so preventing new infections from other patients.

TABLE 3

Second attack of scarlatina.

(First recurrence).

Test period	Year	Series	Treatment				Hosp. weeks	Number scarl. cases	Recurrences							
			From day	Times per day	Admin. inj. i p.os o	Days			Within 6 w.	%	6 w.–3 m.	%	Total	%	>3 months	%
a)	1946–47	*Ka*					6	228	20	8,8	1	0,4	21	9,2	3	1,3
	1946–47	*Pa*	2	8	i	6	6	221	3	1,4	2	0,9	5	2,2	11	5,0
b)	1947–48	*I-K*		–			3	219	2	0,9			2	0,9	2	0,9
	1947–48	Pb_2	2	7, 3, 2	i	6	3	222	3	1,4	2	0,9	5	2,3	21	9,5
	1947–48	Pb_3	5	7, 3, 2	i	6	3	211	1	0,5	2	0,9	3	1,4	9	4,3
c)	1948–49	*Pci*	2	1	i	6	3	260	8	3,1	2	0,7	10	3,8	42	16,2
	1948–49	*Pco*	2	3	o	6	3	255	6	2,4	4	1,5	10	3,9	43	16,9
d)	1949	*Pdi*	2	1	i	6	1	1 669	24	1,4	15	0,9	39	2,3	103	6,2
e)	1950–51	*Pei*	2	1	i	6	1	2 148	25	1,1	22	1,0	47	2,1	117	3,3
	1950–51	*Peo*	2	3	o	6	1	1 029	16	1,6	20	1,9	36	3,5	75	3,8

Test periods *a*, *b* and *c*: solely cases without initial complication
d and *e*: all cases

K control cases. *I-K* isolated control cases (separate rooms)

P penicillin cases: Numerals 2 and 5 day when treatment commenced
Letters i and o penicillin injection and per os.

Within the different penicillin series the early second attacks in the period 0–6 weeks were as a rule about 1–1.5 per cent. After cutting down the time of hospitalization, the result was that the children suffered a second attack at home instead of in hospital. The reason for this must first and foremost be sought in *infection of the home environment* to which the children return. The paradoxical change has thus taken place that the so-called "return" cases, which were encountered earlier when a diseased child returned home and infected its siblings, have now, so to speak, been transformed into the opposite, whereby the patient is infected by his family on his return home and attacked by the disease a second time. The early second attacks could largely be avoided if eradication of infection from the home environment was carried out in respect to hemolytic streptococci.

But there is a factor other than the infection of the environment which must be taken into account as the cause of early second attacks. The possibility exists that the *streptococci may return* because they have been eradicated inadequately and been able to regrow. The patient is reinfected with scarlatina by his own bacteria. For this to happen, the streptococci must be of the same type as in the first attack, and from our experience this can be so.

Early second attacks after different forms of penicillin treatment are shown in Table 3 to be greater when penicillin is administered orally than when given intramuscularly. This is apparent from the extensive test series in the period 1950–51. The difference between *Pei* and *Peo* is 1.4 ± 0.35 per cent for the first three months, 0.5 ± 0.16 per cent for the period 0–6 weeks and 0.9 ± 0.16 per cent from 6 weeks to 3 months. Thus all differences are established statistically.

In a control, one week after discharge, of 92 per cent of 1,280 cases treated, it was found that 6.4 per cent of the injected patients and 14.2 per cent of perorally treated patients manifested a return of hemolytic streptococci. This statistically significant difference (7.8 ± 2.1 per cent) may be of importance. Peroral treatment was inadequate, with the dosage administered, in preventing a rapid new growth of bacteria and the endogenous occurrence of scarlatina to the same degree as when the injection treatment was used.

Thus the investigation shows, with regard to the early second attacks, that the significant factor is not only the infected environment to which the patient returns, but also the preceding treatment. The treatment should clearly be of an intensity sufficient to prevent the return of hemolytic streptococci to the greatest possible extent. The peroral dose administered by us can thus not be considered to have been fully adequate, even if its clinical effect was good. (The dose was therefore increased to obtain better eradication of the bacteria (100,000—200,000 IU pen.-proc. per os × 3)). Control of the return of hemolytic streptococci should be of great importance in the com-

bating of second attacks, and also an indicator of the infectivity of the environment. Provided that therapy has been sufficiently intensive, the frequency of streptococcic carriers will in the main be an expression of the infectivity of the environment. The knowledge of this is of course valuable.

The frequency of second attacks in the period 6 weeks to 3 months varies roughly between 1 and 2 per cent within the penicillin series. At this period the patients have returned to school and institutions of different kinds, so that there is greater opportunity for infection outside the home.

Finally, it is found that no change has occurred in respect to the frequency of early second attacks if one considers the whole of the first quarter following the primary attack. Table 2 shows also that in 1938–42 the frequency was 2.8 per cent and in 1947–51 2.6 per cent.

As regards the *late second attacks*, where the great difference between treated and untreated cases lies, it is evident from the test periods *a* and *b* that the frequency of second attacks was 5 per cent in the penicillin series *Pa*, 1.3 per cent in the control series *Ka*, 9.5 per cent in Pb_2, 4.3 per cent in Pb_5, and 0.9 per cent in the corresponding control series *I-K*. Second attacks were thus about 4, 10.5 and 5 times as many in the various penicillin series.

Of interest is series *c*, in which second attacks comprise no less than 16.2 and 16.9 per cent respectively. This must be because the patients were subjected to particularly violent infection a short time after recovery from scarlatina. These series must in any case be excluded since the epidemic broke out in 1949, so this assumption should be justified. The figure 6.2 per cent for period *d* (1949), series *Pdi*, is also high, particularly when considering the shorter time under observation (cf. Table 3): the reason is that the epidemic continued during 1950.

Naturally we soon began to consider the possibility of trying to prevent these second attacks. The simplest method appeared to be to let the disease run its course a certain time and then commence penicillin treatment, a method which I have called "*postponed treatment*".

The first trials were made in period *b* (1947–48), treatment being commenced on the second and fifth days respectively, series Pb_2 and Pb_5. In the former series there were 9.5 per cent second attacks, in the latter 4.3 per cent. The difference was thus 5.2 ± 4.4 per cent, which may be incidental. I would also point out, however, the great disparity between second attacks in penicillin-treated scarlatina cases and desquamation cases (see Table 2). In the former case it was 4.5 per cent, in the latter 1.7, the difference being 2.8 ± 0.4 per cent. Thus the risk of second attack in patients admitted for scarlet fever exanthema was nearly three times as great as in patients admitted for desquamation. The latter have already passed through the disease in the home even if in a mild form, and have thus had time to acquire a certain immunity.

The postponed treatment now practised consists of deferring treatment until the seventh day. The effect appears to be very satisfactory. The prerequisite for this treatment is that the scarlatina is of a comparatively mild nature and does not give rise to any particular complications within the period when no treatment is administered. In toxic and complicated cases it cannot be adopted, but these constitute at present a small minority. In patients over 15 years the penicillin treatment has also to be instituted at once owing to the greater risk of myocarditis of a more serious character, according to LEVANDER-LINDGREN's investigations of the present material.

Another approach would be to *inoculate with scarlatinal toxin*, simultaneously with penicillin treatment, in an attempt to create immunity by means of an adequate production of antitoxin. Tests have been in progress for about a year, but the results are not yet clear. In comparison with simultaneous series involving immediate and postponed treatment, however, this combined method of treatment and inoculation has not so far exhibited favorable results.

The deterioration in immunity is noticeable in that the patient may have not only one but several second attacks. No less than 27 (5.3 per cent) of the penicillin-treated cases of scarlatina have suffered a *third attack* and two cases a fourth attack. To judge from the penicillin cases the frequency of the third attacks appears to be about the same, whether the second attack belongs to the early or late group. In total the penicillin cases from 1947–51 manifest 4.4 times as many third attacks as the untreated from 1938–42 for only one fourth the time under observation.

Discussion

It has been considered that scarlatina is followed by satisfactory, if not assured, immunity. Second attacks in the form of relapses during the previously long stay in hospital have been common, but were thought to be expressions of cross-infections sustained in hospital due to different types of hemolytic streptococci rather than of immunologic conditions.

The introduction of penicillin made possible an appreciable reduction in the time of treatment, as a result of which, and of the bacterial eradication by penicillin, relapses in hospital have practically disappeared. Despite this, there esists the same marked tendency towards early second attacks—during the first three months—as before the advent of penicillin. The explanation may be that a period unfavorable from the point of view of immunity follows immediately after the first attack. But hemolytic streptococci must recur in the patient if he is to sustain a second attack. Infection from the home environment is here the most important factor. An endogenous mechanism

involving regrowth of the patient's own bacteria may also exist, which is evidenced by the rather more numerous early second attacks in patients treated by the less effective peroral method.

As regards the late second attacks—after three months—the great difference between the pre-penicillin and penicillin epochs becomes apparent. Thus the risk of late second attacks after a mean time of observation of 2½ years in the period 1938–42 was for scarlet fever exanthema cases 0.5 per cent, for desquamation cases 0.3 per cent, while the corresponding figures in 1947–51 were 4.5 and 1.7 per cent respectively, that is 9 and 5.7 times as great respectively.

In three different series of penicillin cases the frequency of second attacks after 4–5 years of observation was 4.3, 5.0 and 9.5 per cent, which was from four to ten times as high a frequency as in the corresponding control series. As a result of an epidemic it was found that the frequency of second attacks in certain series rose to 16–17 per cent after only 2 years of observation.

In the pre-penicillin period second attacks were found mainly among children who had had scarlatina prior to 3 years of age. The risk of a second attack in penicillin-treated patients is much greater after this age and the risk of a second attack has increased progressively with children of rising age. It has thus increased twofold, fourfold and ninefold in the ages 0–3, 4–8 and 9–14 years respectively. Simultaneously with this change the interval between the first and the second attack has become considerably shorter. Previously second attacks were fairly evenly distributed over a period of seven years, but now there is a markedly decreasing tendency from the first to the third year.

The deterioration in immunity is also manifested by the fact that patients undergo recurring attacks of the disease. A third attack was found in 5.3 per cent of cases under observation for a mean period of 2½ years, while from 1938 to 1946, when the period of observation was nearly four times as long, the figure was only 1.2 per cent.

These results harmonize with the assumption of markedly deteriorated immunity, which is all the more pronounced with increasing age in children between 0 and 14 years.

In order to create better immunity and counteract second attacks, attempts with postponed treatment were made. The first series were commenced in 1947–88, and up to 1951 second attacks were experienced in 9.5 per cent of patients treated from the second day, against 4.3 per cent of those treated from the fifth day. The difference is appreciable, but not statistically conclusive. The correctness of the conception is demonstrated, however, by the extensive material from 1947–51, in which there were 4.5 per cent second attacks among scarlatina cases treated with penicillin, while

the corresponding figure for penicillin-treated desquamation cases was only 1.7 per cent. The difference is significant. Desquamation cases have had time to acquire a certain immunity during the first period of illness in the home. Tests being carried out by postponing treatment to the seventh day have up to now also brought very encouraging results.

Another method, involving the combination of penicillin treatment with inoculation with scarlatinal toxin, has, on the contrary, not so far led to any improvement in immunity. From a practical point of view this combined method would be the best solution of the problem. Our experiments in this field will be continued.

The proven deterioration in immunity in treated cases of scarlatina is not of such significance that penicillin therapy should be abolished. Penicillin has from many points of view proved its value. But the deterioration in immunity is of such magnitude, at all events in Stockholm, that it cannot be overlooked. Treatment should therefore be modified so as to have as little effect on immunity as possible. The solution appears to me at the moment to lie in postponed treatment. This procedure can as a rule be adopted in children up to 15 years of age, since scarlatina is at present a comparatively mild disease. In toxic or complicated cases therapy must of course be commenced at the earliest possible moment.

Scarlatina spreads more readily in towns than in the country. Social conditions in Stockholm have during recent years also led to an increased risk of the disease in pre-school age children and thus to an increase both in the number of scarlatina cases and of second attacks. Experience in other parts of the country during the last epidemic showed that there was less risk of a second attack in small towns and in country districts than in Stockholm.

The treatment of scarlatina by penicillin presents an extremely instructive example of immunity following a disease being impaired as a result of the use of a modern antibiotic. The investigation thus has a wider biological aspect, since similar conditions may arise in respect to other diseases. Drugs should not be allowed to interfere too much with the biological processes and thereby provoke a deterioration in our powers of resistance.

Summary

The effect of penicillin on immunity following scarlatina has been investigated. Comparative studies were made of the incidence of second attacks in Stockholm during the pre-penicillin period 1938–46 and during the penicillin period 1947–51. Parallel series in addition comprised treated and untreated cases.

Early second attacks, or relapses, in hospital diminished considerably due to the lesser risk of cross-infections. The frequency of early second attacks within the first three months of recovery was, however, as great as previously. Apart from the pos-

sibility of impaired immunologic conditions during this first period, the factors governing the recurrence of attack at this stage are nowadays the risk of infection from the home environment and also, to some degree, the lack of intensity in treatment. A reduction in the early second attacks should be obtainable as a result of effective treatment and after-control of the patients and of eradication of bacteria from the environment.

As regards the late second attacks (after three months) the frequency was many times higher in 0–14 year-old children who had been treated with penicillin than in the untreated. With increase in age, moreover, the relative frequency of second attacks rose still more. The interval between attacks was much shorter than in the pre-penicillin period. There was thus a marked deterioration in immunity, which was all the more pronounced as the children grew older.

It proved probable that the risk of a new attack of scarlatina could be diminished by postponement of treatment. This is in agreement with the observation that second attacks among penicillin-treated desquamation cases are very much less numerous than among treated cases of scarlatina.

The value of penicillin in the treatment of scarlatina is so great that its use should be continued. The tendency to second attacks, even recurring attacks, is on the other hand so considerable, at least in built-up areas, that a modification in the treatment should be introduced. Postponed treatment can be adopted in all cases in children except those exhibiting markedly toxic symptoms or purulent complications.

Traitement pénicilliné et immunité envers la scarlatine.

L'auteur a recherché l'effet de la pénicilline sur l'immunité qui suit la scarlatine. Des études comparatives ont été faites à Stockholm, sur les conséquences d'une deuxième atteinte de la maladie, l'une avant la période de la pénicilline en 1938–46, l'autre au cours du traitement pénicilliné en 1947–51. Des séries comprenant des cas traités et non traités ont été mis en parallèle. On peut en déduire que le risque d'une nouvelle atteinte par la scarlatine peut être diminué en différant le traitement. Les deuxièmes atteintes parmi les cas traités en période de desquamation semblent beaucoup moins nombreuses que ceux parmi les scarlatines traitées. Le valeur de la pénicilline dans le traitement de la scarlatine est telle que son usage semble devoir être continué. Les récidives, les rechutes, sont si fréquentes, du moins dans les zones urbaines, qu'une modification dans le traitement devrait être introduite. Un traitement différé serait à utiliser chez des enfants dans tous les cas, sauf ceux où l'on note des signes toxiques nets, ou des complications purulentes.

Penicillinbehandlung und Scharlachimmunität.

Die Wirkung des Penicillins auf die Scharlachimmunität wurde untersucht. Vergleichende Untersuchungen über die Häufigkeit von zweiten Erkrankungen sowohl in der Prae-Penicillin-Periode 1938–46 als auch in der Penicillin-Periode 1947–51 wurden durchgeführt. In Parallelserien werden behandelte und unbehandelte Fälle verglichen. Es zeigte sich als wahrscheinlich, daß das Risiko einer erneuten Scharlacherkrankung durch eine verzögerte Behandlung vermindert ist. Dieses stimmt mit der Beobachtung überein, daß erneute Erkrankungen unter den in der Desquamationsphase mit Penicillin behandelten Fällen wesentlich seltener sind als unter den von vornherein behandelten Scharlachfällen. Der Wert der Penicillinbehandlung des Scharlach ist so groß, daß man sie weiterhin durchführen sollte. Die Tendenz zu zweiten und sogar wiederholten Erkrankungen ist andererseits so beträchtlich, daß jeden-

falls in grösseren Städten eine Änderung der Therapie eingeführt werden sollte. Die verzögerte Behandlung kann bei Kindern in allen Fällen, die keine toxischen Symptome oder purulente Komplikationen zeigen, angewandt werden.

Penicilinoterapia e inmunidad contra la escarlatina.

Se ha investigado la influencia del tratamiento con penicilina sobre la inmunidad post-escarlatinosa. Se han hecho estudios comparativos de los casos de reincidencia de la escarlatina en Estocolmo durante el período 1938–46, anterior al uso de la penicilina, y en los años 1947–51 en que se ha utilizado la penicilinoterapia. Se estudiaron paralelamente los casos tratados y los no tratados. Parece probable que el riesgo de una recidiva escarlatinosa puede disminuirse retardando el tratamiento con penicilina. Esto concuerda con la observación de que la reincidencia entre enfermos tratados con penicilina durante el período descamativo es mucho menor que en los tratados precozmente. El valor de la penicilinoterapia en la escarlatina es tan grande, que indudablemente debe seguirse utilizando. Pero la tendencia a la recidiva, y aún a ataques recurrentes, es, por otra parte, tan considerable, por lo menos en las áreas edificadas, que debiera introducirse una modificación en el tratamiento. Una postergación en el uso de la penicilina podría recomendarse en todos aquellos casos que no exhiban síntomas tóxicos graves, o complicaciones de tipo purulento.

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CASE REPORTS

Erythraemic Myelosis (di Guglielmo) in an Infant

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The appearance of nucleated red blood cells in the peripheral blood be due to many different causes.

An increased formation of red blood cells is the reason for the er o- blastosis in anaemic conditions, as for instance in haemolytic anaemia. I - medullary haemopoiesis causes the appearance of nucleated red cells ae blood in diseases involving the bone marrow, as for instance in the leuk: ias and in malignant tumors infiltrating the bone marrow—these are fo of compensatory erythroblastosis.

A primary erythroblastosis is found when the erythropoietic organ self is the site of the disorder. This is called erythraemic myelosis, erythra ia or erythroblastaemia. The condition is also known under the name di G l- mos' disease.

The main symptoms of erythraemia may be those typical of haem tic anaemia. However, the most important sign from the standpoint of differ ial diagnosis is the *reticulocyte count*. One of the most outstanding sig of haemolytic anaemia is the increased reticulocyte value. In erythr nic myelosis this value is low and remains low during the different phases the disease. A comparison between the pathogenesis of the two diseases expl ins this fact. In haemolytic anaemia the erythropoietic organ is primarily un- affected and intact, the anaemia being due to other causes than distu bed blood cell formation. The reticulocytosis is the sign of hyperfunction of an intact blood forming organ due to an increased demand for red blood cells. In erythraemic myelosis on the other hand, the erythropoietic organ is pri- marily affected, its normal function of forming red cells being decreased and consequently there is no reticulocytosis. The appearance of nucleated ed cells in the blood of a patient suffering from erythraemic myelosis does not signify an increased erythropoiesis but is to be considered as the result of the functioning of a pathologically degenerated hyperplastic erythropoietic organ and of extramedullary foci. In the same way, the appearance of pathological white blood cells in the blood of patients suffering from leukaemia, is the resu

of the functioning of a pathologically degenerated leukopoietic organ and of extramedullary foci.

In erythraemia there may be found a leukaemic component also. In these cases part of the leukopoietic system is involved in the morbid degeneration and one finds, simultaneously, erythroblastosis and leukaemic changes in the blood and bone marrow. This form of the disease is called erythroleukaemia. There are cases described which have begun as an erythraemic myelosis and later on developed into a myeloblastic leukaemia (2, 10, 22, 23).

Erythraemic myelosis is considerably less frequent than leukaemia. MOESCHLIN accepted only 5 of the cases published up to 1940. In 1952 SCHWARTZ and HRITCHLOW published reports on 4 cases of their own and on 10 cases from the literature, the erythroleukaemias being excluded. The list of these authors does not, however, cover all the types of the disease reported in the literature. It shows clearly enough, however, the rarity of the disease. The cases reported in the Scandinavian literature seem to belong to the group of erythroblastaemias by EMILE-WEIL and PERLÈS and to the erythroleukaemias.[1]

None of these patients were infants or young children. DI GUGLIELMO in 1928 published an account of a condition in a newborn which he considered an erythraemic myelosis. At that time the clinical entity known to-day as haemolytic disease of the newborn, was not yet recognized. To the modern reader there seems, however, no doubt that this infant was suffering from that disease. There are evident facts which support this assumption: the baby died at the age of three days; it had a severe jaundice and erythroblastosis, both signs being typical of haemolytic disease of the newborn. The grave form of the disease shows an erythroblastosis with as many immature nucleated red cells as in the infant described by DI GUGLIELMO. MENTEN and GAFFNEY reported the case of a boy aged $2\frac{1}{2}$ years with a blood disease of unknown aetiology which they called "immature cell erythraemia". The disease was apparently erythraemic myelosis as described by DI GUGLIELMO. EMERY described a case of erythroblastaemia in a girl, 13 years of age. STRANSKY and QUINTOS, TONIOLO and ANTI, and TANGHERONI have reported cases of erythroleukaemia in children.

In this paper a disease in an infant which was considered to belong to the group of erythraemic myelosis described by DI GUGLIELMO is presented.

The male infant was born on March 1st, 1951, birthweight 3,750 g. The parents and a sister, 6 years old, were well. The baby was jaundiced during the first 3 weeks but the jaundice disappeared without any treatment. When the jaundice disappeared the baby seemed well but gradually he became pale. On May 9, 1951 the infant was admitted to the Pediatric Department of Turku University, at an age of 2 months,

[1] Since the manuscript of this paper was finished NISSEN and SOEBORG-OHLSEN have published in Denmark a case of erythromyelosis in a man, 60 years of age (1953).

TABLE 1.

Date	Hb %	Er. Mill.	C. I.	Nucl. red cells	Ret. %	Leuc.	Eos. %	Bas. %	Neutrophils				Mo. %	Ly. %	Weight
									Jg. %	Stabs %	Polys. %	Myeloc. %			
Ped. Dpt. Turku															
I Admission															
May 9, 1951	16	0.90	0.89	7,000		14,000	1		1	8	35	1	7	47	3,850 g
June 13	59	2.98	1.02	—		11,400									4,200 ,,
II Admission															
July 7	44	2.00	1.10	3,500	0.1 2.9	18,300	1	1	4	7	23		2	62	4,820 ,,
Nov. 6	34	2.36	0.73	1,100		8,100	2	4			30		4	64	8,100 ,,
Nov. 12	65			300	3.8	6,300	4			2	23		9	62	
Nov. 19	82	4.65	0.87	—	0.2	6,200	3			1	22		7	67	7,780 ,,
Children's Clinic Helsinki															
I Admission															
Dec. 13, 1951	78	3.80	1.03	—	0.5	8,300	1			1	34		1	63	8,040 ,,
Feb. 7, 1952	24	0.96	1.25	1,900	0.8	6,100			10	5	30	5		50	8,020 ,,
Feb. 9	14	0.68	1.03		0.1										7,900 ,,
Feb. 10	54	2.35	1.15	3,200	0.4	7,900			3	5	28	1.5		62.5	7,900 ,,
Feb. 25	74	3.34	1.11	600	0.1	5,600	10	3	1	9	20		4	53	8,180 ,,
Feb. 27	80	3.94	1.03	—											
March 10	68	3.20	1.06	—	0.2	10,800	7	1			39.5		4	48.5	8,280 ,,
II Admission															
April 23	39	2.16	0.93	12,000	0.1	14,100	1		10	4	26			59	8,360 ,,
May 26	37	1.51	1.23	19,600	3.6	12,000	1		2	2	29	1	8	57	8,800 ,,
May 30	77	3.51	1.10	23,600		9,000	9		1		19	2	7	62	8,750 ,,
July 14	42	2.27	0.91	11,200	1.5	10,200	3		6	5	26	1	2	57	9,200 ,,

About the course between the data see text.

On Nov. 6, 1951 a continuous transfusion of blood was started, total amount 495 g.
On February 7, 1952 the ACTH course was started.
On February 9 a continuous transfusion of blood, total amount 230 g, was started.
On February 26 the splenectomy was performed.
On May 26 a continuous transfusion of blood was started, total amount 400 g.
The weight list gives an idea concerning the course of the general condition of the child.

TABLE 2.

	Dec. 13, 1951	April 28, 1952
Myeloblasts	—	—
Neutrophilic myelocytes A	—	0.6
„ „ B	1.2	—
„ „ C	5.0	5.2
„ metamyelocytes	5.4	7.2
„ stab cells	—	0.2
„ polysegmented cells	1.0	1.2
Eosinophilic myelocytes A	—	—
„ „ B	—	—
„ „ C	1.0	—
„ metamyelocytes	1.6	0.2
„ stab cells	—	—
„ polysegmented cells	0.8	—
Basophilic granulocytes	—	—
Lymphocytes	7.6	18.4
Monocytes	—	—
Megaloblasts	—	—
Proerythroblasts	2.6	1.4
Erythroblasts	5.6	8.4
Pronormoblasts	7.6	13.8
Basophilic normoblasts	4.6	9.8
Polychromatic normoblasts	11.2	22.4
Ortochromatic „	42.4	2.6
Normoblast nuclei	1.6	6.2
Nucl. red cells resembling reticulum cells	0.4	0.2
Reticulum cells	0.4	2.2
Degenerated cells	—	—
Myeloid-Erythroid ratio	0.2	0.2
Normal red cell nuclei: misshapen red cell nuclei	8.5	1.5

eight 4,860 g. On admission the haemoglobin was 16 %, the erythrocyte count 900,000, 700 nucleated red cells and 13,600 leucocytes. The colour index was 0.89 and never aried much from 1.0. Polychromasia and basophil stippling were noticed in the rythrocytes. The sedimentation rate (mikro Westergren) was 28 mm/1 hour. For the ifferential count see Table 1. The liver and the spleen were moderately enlarged. The R neg. The blood group was A Rh + and the Coombs' test was negative. The mother as A Rh—, with no irregular antibodies in the serum, and the Coombs' test negative. ests of the urine for albumen and glucose were negative. An X-ray examination of he chest was normal. He received altogether 6 blood transfusions, 60–80 g each toether with liver injections and iron. The child was discharged on June 13. The haemoobin was 59 % and there were no nucleated red cells in the peripheral blood.

The child was re-admitted to the same hospital on July 7, 3 weeks after discharge. he haemoglobin was 44 %, the erythrocytes 2 mill., the nucleated red cells 3,800, the

leucocytes 18,000. Blood transfusions, vitamin B_{12}, folic acid, liver and iron treatment caused a temporary improvement only and the patient's condition deteriorated until the Hb value on Nov. 6 was 34 %, with 8,100 nucleated cells of which 1,100 were red cells. The reticulocyte counts were 0.1–2.9 %. The spleen reached the iliac crest. On October 22, a bone marrow puncture was made. In this sample the myelogenous series was normal. The number of nucleated red cells was increased and all maturation forms were represented from proerythroblasts to normoblasts. A roentgenogram of the bone system taken at the beginning of November was normal. On Nov. 9 a continuous blood transfusion was started: transfusion being discontinued on the 12th, when the baby had had 495 g whole blood. On this day the Hb was 65 %, the nucleated red cells were 5/100 of 6,300 leucocytes, the reticulocytes were 3.8 %. This was the highest reticulocyte value ever recorded during the child's illness. A week later the size of the spleen had diminished. The direct van der Bergh reaction was negative, the indirect reaction was positive. The serum bilirubin was 0.4 mg%. The Takata-Ara reaction was normal. At that time the child developed pneumonia and was treated with penicillin. After this the Hb began to drop. Table 1 shows the course of the blood changes whilst in the Turku hospital.

The child was transferred to the Children's Clinic, University of Helsinki, on Dec. 13, 1951, when 9½ months old. On admission to the Children's Clinic the baby weighed 8,040 g. The general condition was good. He was alert and happy. He was afebrile. He was not jaundiced. The spleen was slightly enlarged. Hb 9.35 g % (78 %), the erythrocytes 3,800,000, colour index 1.03, no nucleated red cells, reticulocyte count 0.5 %, leucocytes 8,300, differential count see Table 1. The sedimentation rate (mikro Westergren) was 27 mm/1 hour. The number of nucleated red cells in the bone marrow was greatly increased; basophil stippling was noticed in the normoblasts, Table 2. The mean diameter of the red cells was 8.1 μ, their osmotic resistance 0.42 % beginning haemolysis—0.34 % total haemolysis. The serum cholesterin was 110 mg %, the Takata-Ara reaction was normal. Tests of the urine for glucose and albumen were negative, but later there were traces of albumen occasionally. There was no free HCl in the stomach. X-ray examination of heart, lungs and bone system revealed no abnormalities. The infant's Hb gradually dropped. He was given liver, vitamin B_{12} and iron intravenously, even though the blood and bone marrow findings did not indicate a lack of the antianaemic principle or iron. He was also given a blood transfusion, 200 g, but the effect was only temporary. The child grew tired and lost weight. The skin had a yellowish tint but the sclerae were not icteric. Nucleated red cells appeared in the blood, and the red blood cells showed anisocytosis, mikrocytosis, poikilocytosis, polychromasia and anisochromia. No sphaerocytes were found. The mean diameter of the red cells was 9.1 μ. The reticulocyte count was 0.1–0.8 %. The hypotonic resistance of the red cells decreased to 0.54 % beginning—0.34 total haemolysis, the indirect bilirubin value was 4 mg %, the direct value was 0.6 mg %. Meulengracht was 1:17. The bone marrow finding remained unchanged on January 7 and 18, and February 7. The platelet count, the prothrombin time and the bleeding and coagulation time did not differ much from the normal values during the course of the disease.

The enlarged spleen, the decreased hypotonic resistance of the red cells, the increased indirect bilirubin value, the appearance of nucleated red cells in the blood and finally the bone marrow findings, favoured a diagnosis of haemolytic anaemia. On the other hand there was a consistently low reticulocyte count which made this diagnosis seem less probable. There were no sphaerocytes. The Coombs' test was negative and there were no irregular antibodies in the serum.

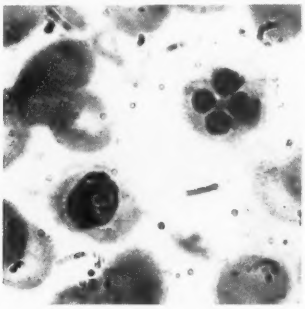

Fig. 1. Peripheral blood. A normal normoblast and a normoblast showing dissociation between the division of nucleus and cytoplasm simulating amitotic division of the nucleus.

On February 7 the Hb value was 2.85 g (24 %), the nucleated red cells were 1,900. The situation was critical and as haemoiytic anaemia seemed the most probable diagnosis the child was given ACTH beginning with 30 mg per day gradually decreasing to 2 mg. After 2 days the haemoglobin had decreased to 1.70 g (14 %). A continuous blood transfusion was started and the following day the Hb was 6.50 g, the nucleated red cells were 3,200. The ACTH was continued, combined with further blood transfusions and the Hb value increased further, the general condition of the child improving amazingly. The ACTH was then gradually decreased.

It seemed obvious, however, that the effect of the ACTH was only transitory and it was decided to perform *splenectomy*. This was done on February 26 and the condition of the child was very satisfactory after the operation. *Histology of the spleen:* Small amounts of haemosiderin, free as well as phagocytised. The connective tissue increased. The follicles medium sized. The endothelium of the veins swollen with vacuolisation beneath the endothelium, but there were also normal veins. No erythro- or myelopoiesis was seen.

The baby was still in good health when discharged on March 11. The Hb was 9.60 g. Since splenectomy there had been no nucleated red cells in the blood. The course of the disease is shown in Table 1. At home the baby remained well until a month later when he developed an upper respiratory infection which was followed by an impairment of the condition.

He was readmitted on April 23, at an age of 1 year 7 weeks, weight 8,300 g. He was pale but alert, afebrile. The Hb was 39 % and there were 12,000 nucleated red cells, most of which were basophilic and polychromatic normoblasts with markedly misshapen nuclei (see Fig. 1). Anisocytosis, polychromasia and basophil stippling present in the normoblasts. The reticulocyte count was 0.1 %. The sedimentation rate was 60 mm/1 hour (mikro Westergren). The leucocyte count was 14,100, the differential count see Table 1. The few myelocytes present were of a mature type and were considered a sign of a compensatory extramedullary myelopoiesis. The direct bilirubin value was 0.20 mg %, the indirect value was 1.45 mg %. The number of nucleated red cells in the bone marrow was greatly increased and all stages of maturation were represented. Attention was drawn particularly to the large number of normoblasts with misshapen nuclei and polychromatic and basophilic cytoplasm. Among the nuclei were seen forms which indicated a dissociation of the division of nucleus and cytoplasm, as described by LEITNER. There was also noticed a high degree of basophil

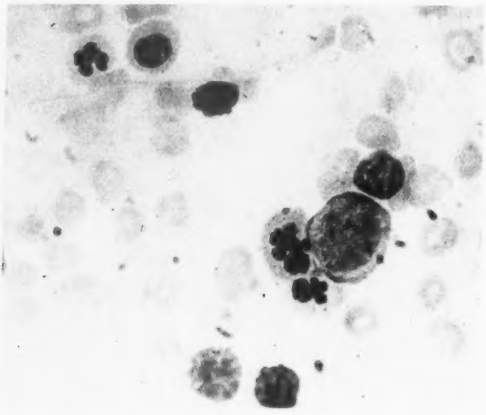

Fig. 2. Bone marrow. Nucleated red blood cells. Normal cells and normoblasts with bizarre and misshapen nuclei.

stippling (see Table 2 and Fig. 2). On the basis of these findings a diagnosis of erythraemic myelosis, di Guglielmo, was made. A re-examination of the previous bone marrow and blood smears showed similar cells, although their number was considerably less (see Table 2). The child was given two blood transfusions but despite this the Hb decreased and on May 26, 5 weeks after admission, the value was only 5.20 g (37 %). The number of nucleated red cells was 19,600. A continuous blood transfusion was started (400 g). The Hb rose to 11.0 g (77 %) but at the same time the nucleated red cells rose to 23,600. After this the Hb fell continuously and on July 14 it was 6.00 g, the nucleated red cells were 11,200 and the leucocytes were 10,200. During his second stay in the hospital the child was given fresh bone marrow with his food regularly, and from the end of June until he was discharged he had folic acid. As he had mild respiratory infections almost all the time, he was given several courses of penicillin and streptomycin. The child was discharged on July 25. His weight was 9,280 g.

The parents were asked to bring him back for examination in 3 weeks. The child however, was doing quite well at home and nothing further was heard of him until the beginning of October, when the mother wrote that the child had died. She said that he had seemed well and happy during the two months after discharge; his appetite had been good and he had been playing out of doors. At the end of September he became feverish, his appetite decreased and he became listless; two weeks later, on October 5, he died. He was then 1 year and 7 months old.

Summary

An infant of 2 months exhibited an anaemia, combined with a hyperplastic reaction of the erythropoietic organs. Nucleated red blood cells were found in the peripheral blood but no reticulocytosis. The spleen was enlarged. In spite of the hyperplasia of the erythropoietic organs no sign of increased erythropoiesis could ever be found. The nucleated red cells showed signs of disturbance in the normal course of matura-

tion, mainly evidenced by a persistent basophilia of the cytoplasm and by severe malformations of the nucleus in a later stage of maturation. No antianaemic agents had any effect on the anaemia and the infant was kept alive by repeated, continuous blood transfusions. He was also given a course of ACTH with apparent good effect. Splenectomy was performed when the child was in good condition after a course of ACTH and continuous transfusion. After this the child was temporarily in comparatively good health but in no better condition than when receiving continuous blood transfusions. The illness lasted for one year and five months after the child was admitted to hospital the first time, and ended with his death.

Myélose érythrémique (maladie de di Guglielmo) chez un jeune enfant.

Un enfant de deux mois présentait une anémie, associée à une réaction hyperplasique des organes érythropoïétiques. Dans le sang périphérique, on trouvait des cellules rouges nuclées, mais pas de réticulocytose. Il existait une splénomégalie. Malgré la réaction hyperplasique des organes érythropoïétiques, on ne trouvait pas de signes périphériques d'une augmentation de l'érythropoïèse. Les cellules rouges nuclées montraient des signes d'un trouble de maturation, notamment une basophilie persistante du cytoplasme, et de grosses anomalies du noyau au dernier stade de la maturation. Les agents antianémiques n'avaient aucun effet sur l'anémie et l'enfant n'était maintenu en vie que par des transfusions répétées. Il fut administré de l'ACTH avec un résultat apparemment bon. Après une amélioration réalisée grâce à l'ACTH et des transfusions continuelles, on tenta une splénectomie. L'état de l'enfant s'améliora de façon temporaire, et ne fut pas meilleur que ce qui avait été obtenu par les transfusions. L'affection dura dixsept mois après l'admission de l'enfant à l'hôpital, et se termina par la mort.

Erythraemische Myelose (di Guglielmo) bei einem Säugling.

Bei einem 2 Monate alten Säugling trat eine Anämie auf, die mit einer hyperplastischen Reaktion des erythropoetischen Organs verbunden war. Im peripheren Blut wurden kernhaltige Erythrocyten gefunden, es bestand aber keine Retikulocytose. Die Milz war vergrößert. Trotz der Hyperplasie des erythropoetischen Organs wurden keine Zeichen einer gesteigerten Erythropoese gefunden. Die kernhaltigen Erythrocyten zeigten Störungen der normalen Reifung, die sich hauptsächlich in einer Basophilie des Cytoplasmas und beträchtlichen Deformierungen des Kernes in späteren Reifungsstadien zu erkennen gab. Antianämische Mittel hatten keine Wirkung, und das Kind wurde durch wiederholte, dauernde Bluttransfusionen am Leben gehalten. Es wurde auch ACTH mit anscheinend gutem Effekt gegeben. Nach wiederholten Bluttransfusionen und ACTH-Behandlung war das Kind in gutem Zustand und die Splenektomie konnte durchgeführt werden. Danach war das Kind zeitweise in ganz gutem Zustand, aber nicht besser als vor der Splenektomie als es mit Bluttransfusionen behandelt wurde. Die Krankheitsdauer betrug 1 Jahr und 5 Monate nach der ersten Klinikaufnahme, und endete mit dem Tod des Kindes.

Mielosis eritrémica (de Guglielmo) en un lactante.

Un lactante de 2 meses de edad presentó anemia acompañada de reacción hiperplástica de los órganos eritropoyéticos. El examen de sangre periférica reveló glóbulos rojos nucleados; no había reticulocitos. Bazo aumentado de tamaño. A pesar de la hiperplasia de los órganos eritropoyéticos, en ningún momento se

observaron signos de eritropoyesis exagerada. Los glóbulos rojos nucleados mostraban signos de alteración en el curso normal de su maduración, principalmente en la forma de persistente basofilia del citoplasma y notorias malformaciones del núcleo en una etapa posterior del proceso de maduración. Ningún agente antianémico ejerció efecto favorable alguno sobre la anemia; el niño era mantenido con vida mediante repetidas transfusiones de sangre. También fué sometido a una cura con ACTH, sin efecto favorable aparente. Después de una serie de inyecciones de ACTH y de transfusiones continuadas, estando el niño en buenas condiciones, se practicó una esplenectomía. Después de la operación el niño gozó durante algún tiempo de comparativamente buena salud, pero no superior al período en que recibía solamente transfusiones sanguíneas continuadas. Desde el ingreso del niño por primera vez al hospital, hasta su muerte, la enfermedad tuvo una duración de un año y cinco meses.

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Sclerema Neonatorum

Report of a Case Treated with ACTH

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Sclerema neonatorum is a rare disease, the principal manifestation of which is hardening of the skin and subcutaneous tissue of the infant. Through the ages the disease has been given many different names and, conversely, diseases of a widely different nature have been designated as sclerema neonatorum. Considerable confusion still persists with regard to the nomenclature. We find that the nomenclature used by HUGHES and HAMMOND (1948) in their survey of this subject is the clearest and most useful, for which reason we have decided mainly to follow the lines laid down by these authors.

Historical

The first description of sclerema neonatorum is usually credited to the Bavarian physician USENBENZIUS, who in 1722 reported a case of "partus octimestris vivus, frigidus et rigidus". During the next two centuries or so a variegated and highly confusing literature on the disease was published. In 1784, UNDERWOOD, of London, gave the first clinical description of the disease, which he named "skinbound". His description aroused interest in the disease, especially in France, where it was termed sclérome. Special importance was attached to the induration of the subcutaneous tissue, for which reason the terms sclérome and sclerema were applied to widely different diseases with this symptom. Most of these cases were actually oedema neonatorum, but such diseases as tetanus and erysipelas neonatorum were also described as sclerema. In addition, a large number of synonyms have been employed; PATERSON (1912) cited about 20. The introduction of the term "sclerodermia neonatorum", especially employed in German-speaking countries and occasionally applied to sclerema, but most commonly to the condition known as adiponecrosis subcutanea neonatorum, added further to the prevailing confusion.

Despite many attempts to clarify the nomenclature (e.g., GRAY, 1933), general agreement has not been attained, and the term sclerema neonatorum is still often applied to a variety of different conditions. Some authors use names such as "sclerema adiposum" and "preagonal induration" for the condition here described as sclerema neonatorum. HUGHES and HAMMOND (1948) deserve great credit for having shown, on the basis of an extensive review of the literature and reports of three additional cases, that sclerema neonatorum is an independent entity, distinct from oedema neonatorum and adiponecrosis subcutanea neonatorum. The great rarity of the condition is illustrated by the fact that they succeeded in finding only 19 absolutely unquestionable cases, including three of their own. In the Scandinavian literature, one case from Norway was briefly reported by LUND in 1950.

Clinical Manifestations

By sclerema neonatorum we understand, like HUGHES and HAMMOND, a disease characterized by a hardening of the skin and subcutaneous tissue, usually of acute onset. The induration usually starts on the thighs and buttocks and spreads rapidly to involve smaller or greater areas of the body. The entire body may be enveloped in a waxlike or cartilaginoid case, so that the infant becomes stiff like a statue. Joint contractures due to the rigidity of the integuments have been described. There is a gradual transition from involved to uninvolved areas. The skin cannot be picked up, and the subcutaneous tissue is bound down to underlying structures. It is a characteristic feature that the skin does not pit on pressure, although oedema may be a precursor of the disease. The colour of the skin is usually pale and yellowish, but occasionally may be red.

Pathology

The pronounced changes in the consistency of the skin and subcutaneous tissue offer a striking contrast to the vague histological changes. HUGHES and HAMMOND, in their extensive review of the literature and report of their own cases, found that histological examinations had been performed in 9 cases only. The only feature which is common to most of these examinations is that there was a more or less pronounced thickening of the connective-tissue bands in the subcutaneous tissue. Inflammatory changes are not seen; BALLANTYNE (1890) is the only writer who, in addition to the connective-tissue changes, has reported slight infiltration of leucocytes around dilated vessels.

Etiology and Pathogenesis

The etiology and pathogenesis of the disease are still unknown. The disease is usually encountered in debilitated, sometimes premature, infants within the first three months of life. Although sclerema neonatorum may be associated with other diseases of the internal organs, there are no constant symptoms suggestive of an internal localization of the condition. The temperature is often subnormal, but normal temperature or even fever has been reported.

In the theory as to the development of the disease which has most frequently been suggested, the importance of chilling, associated with a physiologically lower olein content of the fat of the newborn and the resultant higher melting and solidifying points, has often been emphasized. However, considering that not all infants with sclerema have been exposed to chilling, and that low temperatures in infants are practically never followed by sclerema, this explanation must be regarded as rather improbable. Some reports of studies aiming at demonstrating the presence of an abnormal fat metabolism and abnormal subcutaneous fat in patients with sclerema have appeared, but these investigations are so sporadic and contradictory that they do not offer any explanation for the etiology.

Differential Diagnosis

The most important conditions to be considered in the differential diagnosis are as follows.

Adiponecrosis subcutanea neonatorum (subcutaneous fat necrosis of the newborn) is a disease characterized by sharply circumscribed, firm indurations in the skin an-

subcutaneous tissue occurring post partum, occasionally arising from pressure marks due to a forceps delivery; on the whole, these indurations are most frequently encountered after difficult labour. The individual indurations are often freely movable over the underlying structures. The skin of the involved areas is often red or violet. The disease is due to necrotic degeneration of the subcutaneous fat and may be accompanied by ulceration and, occasionally, calcifications. Fluctuation is sometimes present, and aspiration may then reveal the presence of a thick, milky fluid. Histological examination shows pronounced changes with fat necrosis, inflammatory processes, and foreign body giant cells. The disease does not occur especially in debilitated infants, rather, perhaps, in large infants with abundant amounts of subcutaneous fat. The prognosis is good, spontaneous recovery ensuing in the course of a few months. The disease, which is far more common than sclerema, has been described in detail by several investigators, e.g., BOJLÉN and PETRI. Some investigators claim that this disease, which is often designated as *sclerodermia neonatorum*, is merely a localized or nodular form of sclerema neonatorum.

Oedema neonatorum is to be considered as an ordinary oedema due to some other disease involving, for example, the heart or kidneys. It differs from sclerema in that the skin pits on pressure. The oedematous areas may be very hard, so hard, indeed, that it has sometimes been reported that the skin did not pit on pressure. Accordingly, the disease is not uncommonly described as *scleroedema neonatorum*, but there does not seem to be any reason for maintaining this term, which because of its similarity to sclerema neonatorum is misleading. Nor does the commonly used *sclerema oedematosum* (as distinct from "sclerema adiposum") seem fortunate. Histologically, this form of oedema may be recognized by the loose structure of the tissue, which tends to disintegrate in the sections.

Unquestionable cases of *scleroderma* resembling scleroderma in adults do not seem to have been observed in the newborn. Differentiation from such conditions as *erysipelas neonatorum*, *tetanus neonatorum* and *congenital syphilis* will rarely be difficult.

Treatment

So far, the treatment of sclerema neonatorum has been purely symptomatic. In 1951, KENDIG and TOONE reported a case in which the patient recovered after treatment with cortisone. The treatment was instituted about 48 hours after the onset of the symptoms. Eight intramuscular injections, each of 10 mg, were given; the first three at intervals of 8 hours and the remaining at every 12 hours. As early as 12 hours after the first injection the induration began to subside, and 24 hours later the skin had become normal. In 1952, KENDALL and LEDIS reported a case treated with ACTH. The therapy was commenced 12 hours after the onset of symptoms. A total of 8 injections, each of 5 mg, were given at intervals of 6 hours. A dramatic improvement in the general conditions of the patient occurred after the third injection; the induration began to subside and had disappeared completely 64 hours after the first injection.

Report of Case

A 31-day-old boy was admitted to this clinic in September, 1951, with a diagnosis of congenital debility. The mother was 29 years old and had been in good health during the pregnancy. Spontaneous delivery at full term; vertex presentation, L.O.A.

Obstetric nitrous oxide-chloroform anæsthesia. Birth weight 3000 g; length 49 cm. The child cried vigorously immediately post partum; no asphyxia. The boy was willing to take the breast immediately, but owing to hypogalactia had to be fed a supplementary milk formula. In spite of good appetite and normal stools the infant did not thrive satisfactorily. During the fortnight prior to admission he had had a mild catarrhal infection. On the day of admission he was crying, temperature 38.2° C, and redness and swelling of the right foot and both inguinal regions were noted.

Physical examination on admission revealed a severely affected, slightly dehydrated, pale greyish boy. There was no dyspnoea. The heart action at rest was 200 beats per minute. Auscultation of heart and lungs did not reveal anything abnormal. The weight was 2900 g.

Owing to the poor general condition and the catarrhal infection penicillin therapy was instituted, 60,000 Oxford units being given intramuscularly twice on the first day and from the next day 100,000 units by mouth 4 times daily. During the first 24 hours in hospital the boy whimpered; he was debilitated and had frequent small stools, for which reason medication with aureomycin, 50 mg 4 times daily, was commenced.

At the time of admission, some redness and swelling of the inguinal regions and the lower extremities had been noted. These affections increased in severity the next day, and the skin and subcutaneous tissue of the lower extremities were found to be indurated, leather-like, and superficially scaly, resisting the introduction of the injection needle. The genitalia and the mons pubis were also the seat of hard infiltrations extending across the abdomen up to the level of the umbilicus. Over the thorax and the upper extremities the skin was slightly infiltrated. There was some redness of the lower abdomen and the buttocks. The swelling was most pronounced over the lower abdomen, where there was pitting on pressure. The subcutaneous tissue of the lower extremities was markedly indurated, and here there was also some pitting on pressure, although the consistency was different from that generally felt in oedema.

Fourty hours after admission treatment with ACTH ("Acton"), 5 mg every 12 hours, was instituted. As early as 5 hours after the first injection the skin on the lower extremities became softer, and in the course of the next two days a pronounced improvement occurred. The induration of all involved areas regressed, so that the skin could now be picked up coarsely. At the same time the general condition improved markedly. The ACTH therapy was continued for 9 days, but during the last two days the dosage was reduced to 2.5 mg every 12 hours.

Apart from some paleness for about 15 minutes after the injections, the ACTH therapy did not give rise to any side reactions. The patient did not gain weight during the treatment. Several determinations showed unaffected blood sugar level. Electrocardiographic records did not reveal any evidence of hypopotassæmia (for electrocardiograms, see later). Blood counts showed a distinct fall in eosinophil cells 4 hours after the injections.

Following the progress during the first few days some induration persisted, and this remained unchanged throughout the course of treatment and the next 2–3 weeks. As the pathological changes then began to increase in severity, the ACTH therapy was resumed after a lapse of a month or so. During the second course of treatment two injections daily of 5 mg were given for 13 days. During this period also some improvement occurred, but more slowly and less distinctly than during the first course. Three months after admission some induration still persisted; it began proximal to the ankle joints, increased in severity towards the knees, especially on the anterolateral surfaces, and gradually vanished on the upper part of the thighs. The medial surfaces of the

thighs and the genitalia were not involved at that time, whereas distinct induration was present over the buttocks and back, especially medially, and to a slighter degree, over the abdomen and the lower part of the thorax, the shoulders, arms and the radial surfaces of the forearms. The upper part of the thorax, the neck and face were uninvolved, and the same applied to the hands, although some small indurated plaques in the subcutaneous tissue of the dorsal aspects of the proximal phalanges were present. The involved areas were ill-defined, with gradual transition between affected and unaffected skin. There was no pitting on pressure. The skin could not be picked up; attempts at doing so resulted in the peau d'orange phenomenon. The subcutaneous tissue was also bound down to underlying structures in the most severely affected areas. The skin was pale, smooth and shining.

Even though the histochemical studies reported below did not give evidence in support of the assumption that a beneficial effect on the skin symptoms could be expected by administration of drugs with hyaluronidase effect, treatment with large doses of ascorbic acid was attempted. From about three months after admission the infant was given a daily dose of 0.6 mg of ascorbic acid for 42 days. Although the induration did not completely disappear during this period, it slowly subsided, and this regression also continued after the withdrawal of ascorbic acid.

In addition, the stools, which soon after admission had become liquid, later varied in consistency, but were frequent throughout the hospital stay. Vomiting was rare, but some regurgitation occurred in a certain period. Roentgen examination of the oesophagus showed no pathological changes.

At the age of 2 months a limitation of extension of both knee joints (15–20°) was noted; it persisted during the hospital stay. Roentgenograms of the extremities showed nothing abnormal in the knee joints and normal osseous development of the wrists.

The anterior fontanelle, measuring 2 × 2 fingerbreadths on admission, was found to be closed at 4 months, perhaps indicating premature synosteosis. There was no cranial deformity, and roentgenograms of the skull and ophthalmoscopy showed normal conditions.

During the first month in hospital the patient showed normal psychic development; spontaneous movements were brisk and he could smile, but then the development seemed to come to a standstill. On discharge he was thus extremely oligophrenic; he did not fix his attention on objects or persons or react to sounds. Probably, he could not see and it was, on the whole, difficult to make contact with him. He was flabby, atonic, unable to sit alone or hold up his head, or raise it when placed in the prone position. He did not turn in bed and moved his arms very little.

A few days after admission he had some cyanotic attacks. Similar episodes were not seen later, and there were no other clinical signs of cardiac disease. A roentgenogram showed a heart of normal size and form. On the other hand, electrocardiograms showed changes characteristic of the Wolff–Parkinson–White syndrome, alternating with normal complexes. The electrocardiographic findings have previously been reported by one of us (G.S.).

In addition, it may be stated that the Wassermann reaction and antistreptolysin titre were normal. Serum cholesterol 78 mg%. A serological examination did not reveal any evidence of toxoplasmosis. Micro-sedimentation reaction slightly elevated (min. 9, max. 16); haemoglobin 88–80%. On admission, 53,200 leucocytes per cmm, with a preponderance of neutrophils. Moro's reaction negative. The spinal fluid contained 12/3 while cells and 30/3 red cells (Fuchs–Rosenthal's counting chamber). Globulin 2, albumin 36 (method of Brandberg, Ross and Jones as modified by Bisgaard).

Follow-up examinations. — The patient was discharged at the age of 7 months. At a follow-up examination 5 months later some induration was still present around the knee joints and on the lateral surfaces of the legs, and the skin over the shoulders was also slightly indurated. In these areas the skin was difficult to pick up, but it was freely movable over the underlying tissue. At the age of 17 months, another follow-up examination did not reveal any residual induration.

Histochemical studies. — To determine whether hyaluronidase might influence the pathological skin changes (in analogy with the observations described by ASBOE-HANSEN) Hyalase LEO, 3 D.M.K. units dissolved in 1 ml of water, was injected into the subcutaneous tissue of the right leg. Similarly, a subcutaneous injection of 2 ml of a 2% solution of ascorbic acid was given in the left leg, because this substance has been claimed to have a hyaluronidase-like effect (DAUBENMERKL), although this view is not shared by all writers (see, e.g., REPPERT *et al.*). Some investigators have observed a favourable effect of large doses of ascorbic acid in the treatment of "collagen diseases" (e.g., MASSELL *et al.*). It was observed that the consistency of the skin around the sites of injection became almost normal, but 24 hours later it had returned to the former state.

Biopsy specimens of the skin at the sites of injection were removed 8 hours after the injections. Shortly before, a similar specimen of indurated tissue had been removed from the right thigh for comparative study.

The histological examination of these specimens was kindly performed by Dr. Tage Lund, the Institute of Pathology, Aarhus Municipal Hospital, who also examined preparations stained with special reference to a possible metachromasia of the connective tissue. The stains used were toluidine blue, methylene blue and thionin. Histologically, the epidermis did not reveal distinct changes. The corium was relatively thick with rather plump lamellae. The connective tissue in the corium showed normal cellularity; there were no inflammatory infiltrations; the number of mast cells was scarcely increased, and no metachromasia of the connective tissue could be demonstrated. The corium emitted some septa down through the subcutaneous tissue and formed a fairly well-defined line of demarcation at its junction with a deeper layer of loose finely fibrillar connective tissue; the fibrils were arranged in loose bands running parallel with the surface. The subcutis showed fatty tissue with fairly large, mature cells. There was no necrosis, proliferation of fat cells, inflammatory infiltrations, or granulomata. No precipitates of fatty acid crystals or other salts were seen, and giant cells were absent. Sparse amounts of elastic tissue were present.

The histological picture of the tissue which had been exposed to the action of ascorbic acid was essentially the same. The number of mast cells was unchanged, and there was no distinct metachromasia. In the deeper layers of the skin treated with Hyalase a few scattered leucocytes, but no other cellular infiltrations, were seen, and the tissue did not differ from that of the other specimens.

A histological examination of a biopsy specimen secured after three weeks' treatment with ascorbic acid showed unchanged conditions.

Comments

The case reported above shows good agreement with the definition of sclerema neonatorum used by HUGHES and HAMMOND and several other authors. The disease was characterized by a diffuse, symmetrical hardenin-

of the skin and subcutaneous tissue of acute onset, starting on the lower extremities and the buttocks, gradually involving the greater part of the body and being accompanied by severely impaired general health.

In our patient the disease began somewhat later than in most of the cases reported in the literature, in which the disease most frequently occurred within the first week of life. However, one of HUGHES and HAMMOND's patients was 33 days old at the onset, and HARRISON and MCNEE observed a case in a 70-day-old patient.

Our case does not allow of any conclusions as to the etiology of the disease. It is noteworthy that the patient presented signs of congenital defects, principally encephalopathy evidenced by oligophrenia, microcephalia and pathological spinal fluid with increased protein values. PATERSON mentioned "some cerebellar lesion" in his patient, and one of HUGHES and HAMMOND's patients suffered from microcephalia and convulsions and revealed signs of congenital cardiac disease. However, as no mention was made of congenital defects in the other cases reported in the literature, such defects do not seem to play a role in the pathogenesis of the disease.

As histological examinations were not carried out in our case until after the treatment with ACTH, we cannot say whether or not pathological changes were present during the acute phase of the disease. At the time of the examination the skin was still markedly indurated, but in spite of this it did not reveal any characteristic histological changes, which is in agreement with previous reports.

The prognosis of sclerema neonatorum has so far been very grave; only 5 of the 19 patients mentioned by HUGHES and HAMMOND survived. After the institution of the ACTH therapy a dramatic improvement of the general health of our patient occurred, and at the same time the induration diminished considerably. As KENDALL and KENDIG also obtained good results with ACTH and cortisone, respectively, it is reasonable to hope that these substances will prove to be valuable therapeutic agents in the treatment of sclerema neonatorum.

Summary

A case of sclerema neonatorum in a 4-week-old boy, treated with ACTH with good effect, is reported.

Sclérème des nouveaux-nés. Sur un cas traité par l'ACTH.

Les auteurs rapportent un cas de sclérème des nouveaux-nés, chez un enfant de 4 semaines. Un traitement par l'ACTH a donné de bons résultats.

Sclerema neonatorum. Bericht über einen mit ACTH behandelten Fall.

Es wird über einen Fall von Sclerema neonatorum berichtet, der erfolgreich mit ACTH behandelt wurde.

Esclerema Neonatorum. Caso tratado con ACTH.

Se comunica un caso de esclerema neonatorum en un niño de 4 semanas de edad, tratado favorablemente con ACTH.

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The Danish Paediatric Society

Meeting, January 20, 1954

Chr. Hansted: **Exophthalmic goitre in a girl aged 11 years. Medical and surgical treatment compared.**

Discussion: *Henning Andersen* and *A. Rothe-Meyer* reported some cases treated with propylthiouracil where the results to date had proved satisfactory. *R.-M.* stressed that treatment with thiouracil should be attempted, at any rate in young children, as this therapy does not compromise the result of possible later surgical treatment.

Henning Andersen, Mogens Andreassen and Flemming Quaade: **Biopsy of the testis in children with ectopic testes.**

A short review was given of the scope and technique of biopsy of the testis. Subsequently, the preliminary results of testicular biopsy in 30 boys prior to or at puberty were presented. The objects of the investigation were to elucidate (1) whether the different types of cryptorchism, retention, inversion etc. showed characteristic histological pictures; (2) when possible degeneration of the testis might be revealed; therefore, the histological findings were in all cases considered in relation to the size of the genitalia, the secondary sex development, hormone excretion in urine, etc.; (3) whether previous medication with gonadotrope hormone (Physex) produced histological changes.

The present material showed no histological pictures characteristic of the different types of cryptorchism and no signs of degeneration except in 3 patients who showed signs of endocrine disturbance in addition to cryptorchism. In these cases, the structure of the testes deviated from normal. Physex in doses of 1,000 units × 10 administered from 2 months to approximately 2 years prior to the biopsy caused no histological changes.

Discussion: *Chr. Hansted:* What was the interval between the cessation of treatment with Physex and the testis biopsy? — *Henning Andersen:* One year.

Carl Friderichsen and Johs. Melchior: **The incidence and prognosis of pyrexial convulsions in children, illustrated by 400 cases. Preliminary communication.**

The conception of the prognosis of pyrexial convulsions has undergone a change in character in recent years. American research workers, on the basis of electroencephalography, have concluded that it is distinctly worse, as regards later development of epilepsy, than indicated by the work of Faxén and Herlitz. Follow-up examinations conducted by these authors revealed an incidence of epilepsy of 5—3 per cent. Petermann, however, found dysrhythmia of petit mal and grand mal types in 74 per cent of his cases of pyrexial convulsions and was of the opinion that no normal child suffers from pyrexial convulsions. Lennox considered that the transition from con-

vulsion to epilepsy is fluid. To investigate whether conditions in Denmark correspond to those in the Swedish investigations, a material of 400 cases of pyrexial convulsions in a 15-year period was studied. Forty per cent of the hospital admissions were children under 7 with pyrexia, and 11 per cent of these suffered from pyrexial convulsions. Eighty-three per cent of the 400 children with pyrexial convulsions were in the age group 0—4 years. In 61 per cent of the cases the causal condition was to be found in the rhino-pharynx and the tonsils. The height and sudden onset of the temperature played a role. Replies to questionnaires were received from 300, i.e. 74 per cent. In 3 per cent of the cases, epilepsy developed later. Sixty-seven of the children had one convulsion only and showed no subsequent symptoms. Thirty per cent of the cases had repeated convulsions without subsequent epileptic symptoms; however, 25 per cent of the latter children were described as nervous. The authors mention 6 different criteria which at the very first seizure should arouse suspicion of the diagnosis of epilepsy and indicate observation: (1) prolonged eclamptic seizures; (2) focal convulsions; (3) persistent convulsions despite adequate therapy (4) pyrexial convulsions in children over the age of 5 ;(5) recurrence of convulsions without pyrexia; (6) hereditary disposition.

Ragnhild Bjerglund Andersen and Sven Brandt: **Electroencephalographic findings in children with pyrexial convulsions.**

On electroencephalography, abnormalities were found in 25 per cent of 129 children. The abnormal findings were slightly more frequent in girls than in boys; the highest frequency was encountered among children of 3—4 years of age or slightly older; the abnormal findings were more frequent in children who had had more than one seizure and slightly more frequent after prolonged than after short convulsions; abnormalities were not more frequent in children examined shortly after the seizure than in children examined after the lapse of a longer period. The abnormal findings might disappear, persist or become accentuated, while isolated children with normal EEG's might later develop abnormal EEG's. The electroencephalographic findings indicate that pyrexial convulsions are a form of epilepsy, though mild and with a favourable prognosis. To maintain the old conception that pyrexial convulsions are the childhood equivalent of rigors in adults is unscientific. Electroencephalography may be of assistance to the clinician in selecting those cases which are most prone to become epileptics later, so that anti-epileptic therapy may be instituted in due time. It is recommended that electroencephalography be instituted in all children with pyrexial convulsions during the month following the convulsions.

Ragnhild Bjerglund Andersen, Sven Brandt and Jac. Øster: **The prognosis of convulsions in childhood. The result of a follow-up investigation by questionnaires sent to patients admitted to Queen Louise's Hospital for Children, Copenhagen, in 1925—1930.**

In the years 1925—1929 inclusive, 176 children with convulsions were admitted to Queen Louise's Hospital for Children. Nineteen died during the hospital stay from the causal disease, most frequently bronchopneumonia. Information was obtained from 116 of the 157 survivors. The prognosis was particularly good for 24 children with epileptiform tetanic seizures and also good for 28 children with pyrexial convulsions affect convulsions or "eclampsia", as only one of these two groups had infrequent

convulsions and one of them was under supervision for mental defect; the rest of them were healthy. For children with seizures as part of a more massive organic nervous condition or with delayed intellectual development, the prognosis was very poor: twenty-three had died, 5 were under supervision as mentally defective; one was apparently mentally retarded. For children with suspected or proven cryptogenic epilepsy, the prognosis was somewhat better: of 34 children, 8 had died and 16 were free of seizures after puberty.

Discussion: *A. Rothe-Meyer:* The original conception of relatively favourable prognosis for pyrexial convulsions still seems to hold true. Clinically, 3 per cent of the children with pyrexial convulsions develop epilepsy, and 30 per cent are abnormal encephalographically; these abnormal EEG's do not seem definitely to confirm any stationary (epileptic) condition. Is EEG indicated for an isolated convulsion in a patient 2 or 3 years old if the history is not suspicious? — *Bendt Broager:* EEG examination of completely healthy air-force recruits yielded several abnormal records. Perhaps these indicate only a lower convulsion-threshold and not potential epilepsy. Is there a constant interval between the convulsions during the recording of the EEG? These records would otherwise only have a limited value. — *Mogens Fog.* Information volunteered concerning subsequent convulsions must be misleading, as petit mal and psychomotor fits are frequently overlooked. In the EEG records, differentiation must be made between diffuse dysrhythmias and epileptic curves. Epilepsy may be defined partly by the clinical findings and partly by the EEG. At present, the diagnosis must be based upon the clinical findings, and the establishment of the delimitation between the two definitions must be left to future experience. — *P. Brøstrup:* Perhaps Brandt's material was somewhat selected, since patients referred to Queen Louise's Hospital from other hospitals were particularly suspected of suffering from epilepsy. What are the indications for anti-epileptic treatment of children with pyrexial convulsions? — *Biering:* What is the configuration of the EEG records from a pyrexial child who does not develop convulsions? — *P. Plum:* Favourable effects may be obtained with anti-epileptic therapy in children with dysrhythmia or signs of organic neurologic lesions but without seizures. What is the neurologists' opinion on this subject? — *C. Friderichsen:* Whether EEG should be performed following an isolated convulsion depends upon the age of the child. If the child is more than 3 years old, this should be done in any case. In the evaluation great stress should be laid on the clinical findings and the case-history: the duration of the convulsions, the occurrence of focal symptoms, familial disposition, previous pyrexial convulsions, etc., are of importance. He did not agree with Lennox's statement that an epileptic condition is always present in pyrexial convulsions. — *Brandt:* To an increasing extent, differentiation is being made between specific and non-specific dysrhythmias, but it is difficult to establish the delimitation. Even though several normal individuals show dysrhythmias, this does not imply a diagnosis of epilepsy. It has not proved possible to achieve a constant interval. To a certain extent the material was selected, but no more abnormal EEG's were encountered in the selected part of the material than in the entire material. It is not known whether epilepsy can be prevented by anti-epileptic therapy. Pyrexia produces EEG changes which as a rule disappear. Pyrexia may be employed as a measure to provoke dysrhythmia in patients with latent epilepsy. — *M. Fog:* At present, EEG renders no definite criterion as to whether the patient will become an epileptic, but individuals with specifically abnormal EEG's are more prone to epilepsy although by no means will all develop the condition. In the Neurological Department, Rigshospitalet, Copenhagen, EEG is performed on all children with pyrexial convulsions.

Those with specific dysrhythmias receive anti-epileptic treatment for a variable period, preferably until the EEG is normal. As anti-epileptic preparation, Difhydan (phenantoin) is gradually replacing Phenemal (Luminal).

Sr. Brandt: **Simulated (?) hysteriform cataleptic convulsions in a boy, aged 6 years, suffering from epilepsy.**

A 6 year old boy had a total of 10 grand mal seizures during a 9-month period and showed severe paroxysmal abnormalities in the electroencephalogram. After a prolonged period of freedom from convulsions, while receiving antiepileptic treatment, he developed cataleptic seizures lasting as long as three quarters of an hour and accompanied by analgesia. They could be interrupted by slapping the skin of the abdomen and they ceased when the boy was made to realize that these seizures were regarded as fakes.

Meeting, February 17, 1954

J. Vesterdal: **A case of cystinosis.**

The patient was a boy, aged 5 years and 9 months, with opacity of the corneae, increased blood urea values, albuminuria, and rachitic osseous changes. The urine did not contain cystine. The disease became manifest at the age of one year with imperative thirst as the initial symptom. The renal function has gradually fallen to 7 per cent of normal. The most recent blood urea value was 120 mg %.

S. Borup Jensen: **Laryngo-tracheo-bronchitis in an infant aged 5 weeks.**

An account was given of a case of fulminating tracheobronchitis in an infant aged 5 weeks, which occurred during a sejour in the Paediatric Department, Sundby Hospital, Copenhagen. The patient was treated with bronchoscopy, aspiration, oxedrini tartras (Sympatol), lobeline, oxygen, steam and antibiotics. Sixteen cases of the same condition which were admitted to the Paediatric Department, Sundby Hospital, during the years 1945—53 were briefly reviewed. Out of these patients, 8 died. Since 1950, 6 patients have been treated with bronchoscopy and 2 of these died. Tracheotomy was performed in 3 cases; one patient died. (To be published in *Nord. Med.*)

Discussion: *T. Jersild:* The speaker was convinced that the early institution of bronchoscopy and aspiration of the tenacious secretion had saved the life of the above-mentioned infant. The subsequent intensive treatment with antibiotics with wide spectra (aureomycin), expectorants (Varidase-spray, ipecacuanha, liberal administration of fluid), frequent aspiration via Nélaton's catheter, and oxygen administration undoubtedly prevented the development of secondary atelectasis. Tracheotomy should be reserved for patients with stenosing laryngitis and was therefore not indicated in the present case. In the course of the last 4 years, 11 children with lobular atelectasis were treated in the Paediatric Department, Sundby Hospital. Only one patient died. In 10 of the patients, the atelectasis disappeared during the course of treatment; five patients were cured after 1—3 bronchoscopies, and in the remaining 5 patients, the atelectasis disappeared following suction alone via a rubber catheter making bronchoscopic aspiration unnecessary. Atelectasis is practically always encountered in patients who have died from laryngo-tracheo-bronchitis and in approximately half of the children who have died with a diagnosis of pneumonia. On autopsy

of 178 children, who died with the diagnosis of pneumonia (Sundby Hospital and Blegdamshospital), 43 per cent had atelectasis (Jersild and Riskær: *Acta Pædiatrica* 1951, *40*: 24). And in an unpublished material from the Children's Hospital, Boston, Institute of Pathology (76 patients), most of them died of pneumonia, the rest died of tracheobronchitis—autopsy performed on all of them. The speaker found 61 per cent with atelectasis; of these, 26 per cent had lobular atelectasis. In order to avoid stagnation of secretion in the bronchi with subsequent development of atelectasis which frequently takes a fatal course, particularly in infants, it is of paramount importance that aspiration be performed at an early stage, either by a rubber catheter or, in severe cases, via a bronchoscope. In the Paediatric Department, Sundby Hospital, bronchoscopy has frequently been employed with life-saving effect and all paediatric departments ought, therefore, to be able to carry out this treatment.

J. Arnrig: **Deafness and severe impairment of hearing in children. Care and etiology.**

1. *Care.* — Following a historical account of the development of the instruction of deaf-mutes, the Law of January 27th, 1950, was mentioned. This law concerns the measures for those suffering from deafness and impairment of hearing. Under the auspices of the Ministry of Social Affairs, a Committee for Individuals with Impaired Hearing and a Committee for Deaf Individuals have been established with the task of handling the problems of those suffering from impaired hearing and deafness, respectively. Under the auspices of the Committee for the Deaf there has been established a National Research and Advisory Clinic for Children Suffering from Deafness or Severe Impairment of Hearing, with headquarters in Copenhagen. Cases with suspected defective speech connected with reduced or abolished hearing in children should be brought to the attention of the Committee for the Deaf as early as possible (i.e. as a rule beginning at the age of 2 years). This Committee arranges for a teacher for the deaf to visit the child's home and for more detailed examination. The examination, as a rule, lasts for several days and the expenditure is a national concern. The child is examined by a psychologist, an acoustician and an E.N.T. specialist and the parents receive medical and paedagogic instruction, in addition to information concerning instruction of the child in hearing, training and lip reading. Suitable children are referred for hearing aids. The child's progress in the home is controlled by visiting teachers for the deaf. Prior to school age, a decision is made whether the child should attend an ordinary school, a school for children with impaired hearing, or a deaf school.

2. *Etiology.* — The material comprises 484 pupils from the three national boarding schools for deaf and one private day school for the duration of the academic year 1952—53. There was a preponderance of males (55 %). The etiological factors could be divided into the following principal groups: 1. Hereditary affection of hearing, 28.5 %; 2. Affections of hearing acquired prior to delivery, 8.7 %; 3. Affections of hearing acquired during delivery, 10.1 %; 4. Affections of hearing acquired in childhood, 31.6 %; 5. Not classifiable, 21.1 %. Each group was accounted for separately in detail, and the relative incidence of the various etiological factors within each group was illustrated by tables. (To be published in *Ugeskrift for Læger.*)

J. Falbe-Hansen: **Impairment of hearing in children. Causes and treatment.**

The causes of hereditary congenital deafness are sporadic recessive deafness, chronic labyrinthine impairment of hearing, sporadic cretinism, and erythroblastosis foetalis.

The causes of congenital, non-hereditary deafness are: disease of the mother during pregnancy (rubella, morbilli, parotitis, poliomyelitis and syphilis), influence by radiation (roentgen, radium and atom bomb radiation), intoxications (quinine, cortisone and carbon monoxide), and factors influencing the infant during delivery (traumata and anoxia). Acquired deafness is most frequently due to meningitis and skull injuries. Congenital impairment of hearing may be due to the same causes as deafness or to congenital malformation of the external and/or middle ear and, very rarely, to otosclerosis. Acquired impairment of hearing is most frequently due to inflammatory or catarrhal conditions in the middle ear and more rarely to conditions in the external ear (inflammation, eczemata and foreign bodies). Not uncommon causes are basal fracture of the skull, sound injuries, labyrinthine concussion, and meningitis. Very rare causes are cerebral tumour and brain abscess. Finally, a reveiw was given concerning the prophylaxis during school age, together with a brief description of modern methods of testing hearing (group audiometry).

H. Chr. Rudolph: **The instruction of school children with impaired hearing.**

The regulations for instruction of children with impaired hearing within and outside Copenhagen were mentioned and an account was given of the Municipality of Copenhagen School for Children with Impaired Hearing which was established on September 1st, 1916. At present, the school comprises 9 classes with 130 children. The task of the school is to offer instruction which supplies the handicapped child the same knowledge as the normal child and to train in lip reading to supplement the defective hearing. In this way the child may learn to understand the spoken word, and by suitable care and advice on ear hygiene the best possible conditions obtain to improve their hearing ability. Approximately half of the children are in possession of individual hearing aids. In addition to instruction in the ordinary school subjects and lip reading, the children receive instruction in speaking; this latter is supplied both as class instruction and, where the most severe cases are concerned, as instruction for small groups of 3—4 pupils. These classes, of half an hour every second day, are held prior to the regular school hours. Extended instruction in Danish is offered to special groups of children with milder difficulties in reading prior to school hours. Special training in hearing is not supplied. In the school clinic, children with suppurating otitis media, sinusitis etc., are treated according to accepted medical principles. On leaving school, the children are given advice about choice of employment, regard being taken of the nature and degree of impairment of hearing. They are subjected to psychotechnical tests, and an index card concerning employment is kept for each child.

Discussion: *P. Plum:* In how many children was aphasia demonstrated in addition to impairment of hearing? — *J. Flamand-Christensen:* As regards prematurity as etiological factor in impairment of hearing, the etiological factors of the prematurity are presumably also the cause of the defect hearing. — *P. Bræstrup:* What are the general principles for the treatment of children with impaired hearing outside Copenhagen? — *J. Arnvig:* Cases of pure aphasia are rare, but the combination aphasia and impaired hearing is a more frequent occurrence. Electroencephalography was not included in the examination but would be extremely valuable in several cases. The question whether it be possible to distinguish functional impairment of hearing from genuine impairment can be answered in the affirmative. Functional impairment of hearing of the order concerned here is very rare. One of the most suitable methods of disclosing these conditions is the so-called psycho-galvanic skin resistance test. The

method, which is applicable both in small children and in adults, is based upon the principle of conditioned reflexes. A sound is produced followed by a small galvanic stimulus. If the sound be perceived, a slight secretion of sweat gradually appears in the palms of the hands and soles of the feet in anticipation of the stimulus to follow. The resistance of the skin in these regions, where it can be registered with the aid of a galvanometer, will therefore oscillate when the sound is heard and an "audiogram" may be recorded. A history of prematurity occurs to a much greater extent among patients with impairment of hearing than among individuals with normal hearing. The etiology is very difficult to clarify; on the one hand it is conceivable that the organ of hearing in the premature infant is particularly vulnerable for conditions such as oxygen deficiency, feeding difficulties, fall in temperature or, as mentioned by Falbe-Hansen, influence by sound. On the other hand, it may also be conceivable that the injury to the organ of hearing (and possibly injury to other organs) and the premature delivery have a common origin, as is probably very often the case when the mother is infected with German measles at the commencement of the pregnancy. — *J. Falbe-Hansen:* There are no children suffering from aphasia in the school for children with impaired hearing. There are quite a considerable number of premature infants among those with impaired hearing. Follow-up examination of a larger material of premature infants was proposed. The task to treat all these deaf children is very comprehensive and practising otologists cannot do it on account of lack of time. A series of school hearing clinics is necessary.

Meeting, March 11, 1954

Knud Wilken-Jensen: **Rhinopathies in allergic children.**

Out of 512 new patients examined in the out-patient clinic for children with allergic diseases, Rigshospitalet, Copenhagen, during the period 1.1 1950 to 1.4. 1952, 225 had symptoms of rhinopathies of the following types: allergic rhinitis (143), hay-fever (15), adenoid vegetations (55), and/or sinusitis (65). The treatment instituted consisted principally of desensitization and elimination, possibly supplemented by removal of the adenoid vegetations and psychotherapy. With a period of observation of 1—3 years, the results of the treatment were found to be as follows: of the 207 patients from whom information is available, 151 showed a satisfactory result, 37 distinct improvement and only 19 patients doubtful or no improvement. By and large, the improvement of the nasal symptoms was accompanied by a corresponding improvement in attacks of asthma or bronchitis which, in the majority of cases, were the cause of attendance in the out-patient clinic. It appeared to be very important that the treatment be prolonged and regular.

Discussion: — *P. Bræstrup* and *Oluf Andersen:* These speakers were very sceptical as regards the validity of this good result. Information was requested to prove whether the rhinitis in these children had disappeared. A cessation of symptoms for a shorter or longer period may be supposed to depend upon purely psychic causes. It was questioned whether specific desensitization was concerned here. — *K. Wilken-Jensen:* The attacks may be caused both by mental and allergic factors but it was not possible to differentiate these groups from one another. It was impossible to state whether the rhinitis has disappeared, since the account is based largely upon a questionary sent to the general practitioners.

Jørgen Kringelbach: **A case of congenital tuberculosis.**

A case of congenital tuberculosis is recorded in a premature girl (birth weight 2,250 g), the only child of a 23 year old mother suffering from miliary tuberculosis. The infant showed signs of central respiratory involvement at the age of 23 days. Moro was positive at 25 days of age (not tested previously), and the cerebral spinal fluid contained 77/3 cells (Fuchs-Rosenthal's counting chamber), predominantly monocytes. Treatment with DHS, PAS and INH was initiated. During treatment the pulmonary changes progressed but the spinal fluid became normal; tuberculous otitis media, cervical adenitis and changes in the eyes developed. Tubercle bacilli were demonstrated in purulent discharge from the ear and in stomach washings but not in the spinal fluid. A critical period occurred when the infant was about 2 months old; during this period the tuberculin test was negative. The crisis was overcome and the infant is at present thriving and developing satisfactorily. She was transferred to another hospital at the age of 4 months. (To be published in *Ugeskrift for Læger.*)

Discussion: The indications for the various antibiotics were mentioned and *Oluf Andersen* referred to recent investigations indicating that 0.5 g streptomycin + 0.5 g dihydrostreptomycin exert the same antibacterial effect but are less toxic than is 1 g of each of the two drugs administered separately.

Torben Jersild: **A case of poisoning with diethyl-para-nitro-phenyl-thiophosphate.**

During the 1939—45 war, a new group of insecticides was produced in Germany, comprizing the so-called alkyl polyphosphates. Among these, diethyl-para-nitro-phenyl-thiophosphate (DPTF) in particular has been increasingly employed in farming, gardening and fruit production to combat plant diseases and vermin. DPTF is readily absorbed from the skin and through the lungs. Like physostigmine and prostigmine, DPTF inhibits cholinesterase. The symptoms of intoxication are: fibrillary muscle contractions, contraction of the pupils, increased peristalsis, and increased secretion of sputum and bronchial mucous, i.e., effects partly of nicotine and partly of muscarine. Atropine exerts an antagonistic effect.

Case-history: A girl aged 2 years was admitted in unconscious condition to the Paediatric Department, Sundby Hospital. She was cyanotic, apparently moribund with rattling respiration and sero-sanguinous, foaming secretion from the nose and the mouth. The pupils were small and did not react to light and unmistakable vertical nystagmus was observed. The extremities were completely relaxed (slight fibrillary muscle contractions were not observed until 3 hours later). As the clinical symptoms aroused suspicion of DPTF poisoning, 1 mg atropine was immediately administered subcutaneously. Twenty minutes later, the pulmonary oedema had disappeared and after 5 hours the child had completely regained consciousness. She was discharged after 5 days in hospital. It was later found out that the father, a gardener, at 11.00 a.m. (i.e. 14 hours prior to the appearance of the first symptoms) had placed his daughter outside a greenhouse where she had been playing with some "empty" cardboard boxes containing azobenzol (to a great extent consisting of parathion). At 1.00 a.m. (i.e. 4 hours prior to admission) the patient complained of pain in the stomach and vomited once. Shortly afterwards she fell asleep. Three hours later the child was unconscious and had rattling respiration. A similar case of poisoning was mentioned which occurred in a gardener, aged 28 years, who had employed "Bladan" as insecticide spray. He was admitted to Blegdamshospitalet with the diagnosis acute gastroen-

neritis (this case has been published previously in *Acta pharmacologica 5:*129, 1949). It should be noted that *in both the cases of DPTF poisoning mentioned above, a long symptomfree interval was present.* In the case of the gardener 7 hours elapsed, and in the case of the child 14 hours, until the first symptoms of poisoning appeared.

Carl Friderichsen: **Announcement of the International Congress in 1956.**

Povl Hertz: **Paediatric causerie about "old times".**

(To be published in *Ugeskrift for Læger.*)

Proceedings of the Section for Pediatrics and School Hygiene of the Swedish Medical Society

Meeting, January 15, 1954

P. Karlberg: **Studies of the respiration in newborns.**

(To be published elsewhere.)

R. Zetterström: **Clinical observations in newborn infants of diabetic mothers.**

The clinical signs and the pathological-anatomical lesions in newborn babies of diabetic mothers are in part similar to those seen in morbus haemolyticus neonatorum. The abnormally high number of normoblasts that can be demonstrated in a great number of newborns of diabetic mothers is supposed to be the consequence of increased erythropoesis due to the effort of the foetus to increase the oxygen capacity of the blood. As proof of this supposition a decreased oxygen tension in the umbilical vein has been shown. Children of diabetic mothers have been considered to have an abnormally large heart volume. This is probably dependent upon the fact that the normal post-natal reduction of the heart volume is delayed as long as there are signs of decreased vitality. Since these children have at birth a strong tendency to edema, they are usually being given no food for two to four days after birth. The electrolyte balance during this period of starvation has been studied. These examinations have not given support to the view that disturbance of the post-natal sodium and potassium balance is the cause of decreased vitality in these babies. During the periods of starvation the blood sugar has generally gradually increased.

Discussion: *B. Björklund* reported the urine excretion of 11-oxysteroids, according to Sprechler, in 8 children of diabetic mothers. No importance had been attached to the absolute values, but there was a tendency to higher values per square meter of body surface area per 24 hours during the first week of life than during the second week of life. In normal infants there is generally a significant increase of the output of 11-oxysteroids from the first to the second week of life, in premature as well as in full-term babies. — *L. Bastman-Heiskanen* reported a statistical survey of the mortality of infants of diabetic mothers, collected from all the maternity hospitals and the children's hospitals in Stockholm during the years 1940–1949, and of prediabetic pregnancies during the years 1893–1945. — *C. G. Bergstrand* stated that the observations which Zetterström had made in embryopathia diabetica speak in favour of an

anoxia in the foetus and the newborn and thought it reasonable to suppose that the etiology is a lesion of the placenta in the diabetic mothers. In some cases reported by Zetterström the placenta was examined histologically, but no pathological lesions was found. The normal values are not known for the excretion of 11-oxysteroids in the urine of newborn babies with the method used by Björklund. One must warn against drawing conclusions regarding the functions of the adrenals from such determinations.

N. O. Ericsson and *Ulf Rudhe:* **Cholangiography in newborns.**

Since 1952 cholangiography has been used in the pediatric clinic of Karolinska sjukhuset as a routine method of exploration of the biliary ducts in newborns. Two to four ml of 35 per cent Umbradil (Astra) were injected slowly into the gall bladder without dissection of the biliary ducts. Immediately after the injection anterior-posterior and oblique exposures were made, preferably in apnoea and with a very short exposure time (4/100 sec.). In order to visualize the intrahepatic ducts a new injection with concomitant compression of the common duct was sometimes necessary. The authors have studied the normal anatomy of the biliary ducts in newborns and made cholangiograms from 8 cases of obstruction of the ducts surgically treated. Two cases of cirrhosis with intact biliary ducts have also been examined. The cholangiographic diagnoses have been verified in cases that have been examined at autopsy.

Discussion: *E. Landelius* reported 27 cases of obvious or suspected biliary atresia. Cholangiography should be used at operation if there is suspicion of occlusion of the deep biliary ducts in infants, but this examination does not exclude an obstruction. The gall bladder and the cystic duct may be damaged, but otherwise no complications have occurred.

R. Zetterström: **Case of hitherto unknown disease of the skeleton (Osteodysmetamorphosis foetalis).**

(To be published in *Journal of Pediatrics.*)

Meeting, February 12, 1954

B. Rydenstam: **Some cases of remission in acute leukemia.**

Report of three cases of acute leukemia in 3–5 year-old children, one of myeloid and two of lymphatic type, which had spontaneous remission up to three months' duration with clinical freedom from symptoms and normalizing of the peripheral blood picture and bone marrow. All three cases were fatal. The case that survived the longest time lived 8 months after the start of the disease.

J. Ström: **The question of the antagonism between penicillin and aureomycin, in the light of therapeutical trials in scarlet fever.**

(To be published elsewhere.)

E. Bengtsson and G. Örndahl: **Complications in parotitis.**

Report on the cases of parotitis treated in Stockholm's Hospital for Contagious Diseases in 1950–52. ECG had been made every week. EEG and lumbar puncture had

been carried out in all cases. Forty-six per cent showed signs of meningo-encephalitis. This complication was not more frequent in orchitis cases. Pathological ECG-changes occurred in 2.3 % of the total group; in 6.2 % of these with encephalitis, and in 8.5 % if both encephalitis and orchitis occurred. The myocarditis started in the 1st–3rd week and had a duration of 3–4(–6) months. Tachycardia occurred in one case, also with enlargement of the heart. Some cases were complicated by neuritis and oophoritis. There was no case of severe pancreatitis. A certain relationship could be shown between carditis and meningoencephalitis, because 92 % of all patients with pathological ECG had a meningoencephalitis.

Discussion: *U. Nordwall:* Has Stilbol any value as prophylaxis against orchitis? — *J. Ström:* An investigation is going on at our hospital regarding the treatment of orchitis with Stilbol, but so far the treatment has had no effect at all.

B. Rydenstam: **Two cases of acute cerebellar ataxia; probably poliomyelitis infection.**

A report of two cases with sudden onset of ataxia, walking disturbance, intention tremor, difficulty in talking and nystagmus. One of the cases was a 5 year-old girl, the other a 3 year-old boy. Both had a benign course with rapid improvement of the symptoms. In one of the cases the spinal fluid was normal, in the other there were 7 cells/cmm. In both cases the etiology was probably encephalitis due to poliomyelitis virus, type Brunhilde, because the serological reactions were significant.

Discussion: *W. Wernstedt:* In the 1911 epidemic of poliomyelitis, cases with ataxia of cerebellar type were not infrequent. — *P. Hedlund:* The results of the examination of the stools are not more significant than the serological tests that have already been carried out. A positive culture from the stools during an epidemic does not indicate that poliomyelitis is the etiology of the disease.

S. Jorup: **Paralytic poliomyelitis without spinal fluid changes.**

Out of 637 cases of poliomyelitis with paralyses, treated at the Stockholm's Hospital for Contagious Diseases from the epidemic of 1953, 30 (4.7 %) had a number of cells in the spinal fluid of 5 per cmm or less and 15 of these cases showed an amount of albumen of 50 mg % or less. Out of 327 non-paralytic cases 13 had a cell content of 5 or less and of these, 8 had an albumen content of 50 mg % or less.

Discussion: *A. Wallgren* mentions an investigation from Drammen in which there was a report on 60 children that had been admitted to the hospital as having poliomyelitis but had been discharged with other diagnoses because of a normal spinal fluid. At a follow-up study 6 of these cases later showed paralyses. One must be careful in excluding poliomyelitis because of a normal spinal fluid.

Meeting, March 12, 1954

E. Jacobsson **and** *F. Wahlgren:* **Case of tuberculosis of peculiar type and development in a BCG-vaccinated child.**

A boy, 6½ years old, fell ill with fever and lymphadenitis of the neck. Tuberculous etiology was not believed to be probable because he had been vaccinated at birth. Strong positive toxoplasmosis tests as well as cutaneous and serological tests indicated concomitant toxoplasmosis infection. Tuberculin tests in the beginning of the disease were only slightly positive but a biopsy of a gland showed masses of acid-fast

rods. The pathologic-anatomical picture was dominated by epitheloid cells and giant cells without caseous necrosis or lymphocytic infiltration; a picture similar to that in Morbus Schaumann if one excludes the presence of acid-fast rods. Streptomycin treatment combined with PAS had in the beginning a good effect, but liquefaction and fistulization of the gland occurred. Culture showed human tb-bacilli. Two years after the start of the disease there was a miliary tuberculosis, which is now treated with streptomycin, PAS and isoniacid.

Discussion: *E. Mannheimer:* The tuberculin test had not been read after 72 hours.—*E. Hagberg:* Was the information of the mother verified that the child after BCG-vaccination has become tuberculin positive?—*B. Vahlquist* had seen a similar case of pulmonary tuberculosis and mediastinal adenitis with a rapid course in which the tuberculin sensitivity was very slight. This child had also been BCG-inoculated. A cousin to the mother had had tuberculosis, but exposure was denied.—*O. Sievers:* After isoniacid treatment in tuberculosis, it has been observed in America, England and in Gothenburg that the guinea pig test turns out negative although the bacteria have grown on Loewenstein milieu.—*G. Jacobsohn:* Can one believe that the biopsy had something to do with the malign course of the disease?

H. O. Mossberg: Case of acrodynia.

Up to 1950 there were about 1,500 cases of acrodynia reported in the literature, of which most were from western Europe. Five cases have during the last 12 years been treated at the *Samariten* Children's Hospital, 3 girls and 2 boys, all of them below 6 years of age. The morbid picture is variable, with adynamia as the most constant symptom. In 3 of the cases there had been a previous virus infection, probably of etiological importance. The pyruvic-acid values were increased in 4 cases; they decreased during vitamine B treatment. There was increased Hg excretion in the urine in 2 cases, one of them showing a positive cutaneous test with Hg ointment. The profession of the father, a dentist, in this case made Hg exposure suspect, but this could not be verified. The etiology and pathogenesis of the disease was discussed. It is probably to be regarded as a functional disturbance of the central regulation of the autonomic nervous system, produced by infectious or toxic agents. The modern "stress" theory is insufficient to explain the whole acrodynia syndrome.

Discussion: *H. Lichtenstein:* The works of Warkany support the theory of the importance of Hg intoxication.

E. Jacobsson: Necroses in BCG-vaccination.

In two groups, each comprising about 300 cases, BCG inoculation was performed in one case subcutaneously, in the other intracutaneously. The doses in both groups were 0.05 mg. In the former group there was a secretion and/or necrosis of some importance in 50 per cent of the cases, severe in 16 per cent, against only 9 per cent local reactions in the intracutaneous group, of which 2 per cent was tabulated as more severe reactions. In the subcutaneous group with the strong local reactions the frequency of tuberculin positives was not greater than in the intracutaneous group.

Discussion: *O. Sievers:* The increased frequency of necroses in subcutaneous injections has been well known for about 20 years and it is always recommended that the vaccine should be given intracutaneously. The BCG-vaccine is sensitive to day light. The Swedish vaccine is at present distributed in red bottles which protects it against day light. The strength of the Swedish vaccine was increased in Octobe

1950. This produced an increased incidence of secretions at the site of vaccination, which has been demonstrated in a publication from Ireland, where Swedish vaccine has been used. At the same time as the cases with secretion increased, the conversion rate of tuberculin reaction increased from 95.16 per cent to 96.27 per cent and one year later to 98.4 per cent. The total number of vaccinated persons is about 88,000 and necroses have not been observed in this series. In tests with the Swedish vaccine in Paris necroses were observed in a frequency below 1 per cent.—*J. Lind:* Out of 200 newborn infants, BCG vaccinated intracutaneously at the maternity hospital, there was not one single abscess or secretion. Out of 60 newborns which had been BCG vaccinated and the mother had tuberculosis there were fewer positives after the vaccination, and the infants became sensitive after a longer interval than in a group of the same size where the father had tuberculosis. The existence of passively transmitted antibodies could, however, be shown only in one case belonging to the former group.—*E. Hagberg* reported a series of 4,200 vaccinated infants with an incidence of necroses of 1.8 per cent. In a group of 1,100 vaccinated older children the necroses occurred in 4.4 per cent of the cases.—*A. Gunther:* The vaccination by means of intracutaneous injection and scarification was compared. There were no local reactions in the children vaccinated by scarification. The persistence of the tuberculin sensitivity was followed during 7–8 years; there was no significant difference between the two groups.—*J. Lind* reported a series of newborns, where scarification and intracutaneous vaccination were compared. Only 60 per cent of the former gave positive tuberculin tests, as against 90 per cent in the intracutaneous group.

Y. Lindblad: **About conjunctivitis and lacrimal duct anomalies in early infancy.**

The congenital stenoses are rather frequent, later stenoses seldom develop in children, for instance in connection with adenoid vegetations. An increased secretion of tears can also be the result of increased production of tears, e.g. in blepharo-conjunctivitis. A congenital stenosis should be suspected if a conjunctivitis persists for 2–3 weeks after birth, and especially if the eye remains humid. One should not omit to press on the lacrimal sac in order to put out any possible secretion, which verifies the diagnosis.

Discussion: *S. Salén:* At the first visit to the Infant Welfare Center the children are often a couple of months old. The home visiting nurses, who see the children earlier, should be instructed as to the condition of the eyes.

N. Malmberg: **Johan Gabriel Collin and his contributions to Swedish pediatrics.**

Through his work "Treaties on children's diseases", published 1841–1851 in 4 volumes, Johan Gabriel Collin has created an important position for himself in the history of Swedish pediatrics. A scanty scientific training and a large amount of practical work as a physician did not prevent him from publishing many scientific works. His publications, except the "Treaties" mentioned, contained among other things the mortality in childhood, and nutritional problems. He was honoured with the title of professor, received an honorary medical degree and was elected a member of the Royal Academy of Science.

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NEWS AND COMMENTS

The XI Nordic Congress of Pediatrics will be held in Oslo, Norway, June 28—July 1 1954. Professor Leif Salomonsen is President, Dr. Arne Nja General Secretary.

The principal subjects chosen for discussion are: "*Cerebral Paralysis*" with reports by L. Salomonsen and M. Skatvedt from Norway and P. Plum from Denmark. "The Electrolyte Balance in Dehydrated Infants" with reports by B. Friis-Hansen from Denmark and N. Hallman from Finland. "Neonatal Asphyxia" with reports by R. Zetterström from Sweden, E. K. Ahvenainen from Finland and W. Blystad from Norway.

There will be a Round Table discussion June 30th on "Physical Diagnosis in Congenital Heart Disease"; moderator E. Mannheimer from Sweden; panel: I. Boesen, Denmark, L.-E. Carlgren, G. Ekström, B. Jonsson and T. Möller, Sweden, O. Husom, Norway and B. Landtman, Finland. The afternoon session of the same day is scheduled for free subjects.

Die diesjährige Tagung der Deutschen Gesellschaft für Kinderheilkunde findet vom 6.—9.9.1954 in Essen statt. President Prof. Bossert, Essen.

Als Rahmenthemen sind gewählt:

1. (Gemeinschaftlich mit der Deutschen Vereinigung für Jugendpsychiatrie)
   a) Der Einfluss der präpuberalen Phase auf die Entwicklung des Kindes.
   b) Die Bedeutung der Kriegs- und Nachkriegszeit auf die Entwicklung des Kindes.
2. Der kindliche Rheumatismus.
3. Erkrankungen des Magen-Darmtraktus und der Bauchspeicheldrüse.